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ASTHMA AND WHEEZING IN THE FIRST SIX YEARS OF LIFE

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Abstract *Background.* Many young children wheeze during viral respiratory infections, but the pathogenesis of these episodes and their relation to the development of asthma later in life are not well understood.

Methods. In a prospective study, we investigated the factors affecting wheezing before the age of three years and their relation to wheezing at six years of age. Of 1246 newborns in the Tucson, Arizona, area enrolled between May 1980 and October 1984, follow-up data at both three and six years of age were available for 826. For these children, assessments in infancy included measurement of cord-serum IgE levels (measured in 750 children), pulmonary-function testing before any lower respiratory tract illness had occurred (125), measurement of serum IgE levels at nine months of age (672), and questionnaires completed by the children's parents when the children were one year old (800). Assessments at six years of age included measurement of serum IgE levels (in 460), pulmonary-function testing (526), and skin allergy testing (629).

Results. At the age of six years, 425 children (51.5 percent) had never wheezed, 164 (19.9 percent) had had at least one lower respiratory tract illness with wheezing during the first three years of life but had no wheezing at six years of age, 124 (15.0 percent) had no wheezing before the age of three years but had wheezing at the age of six years, and 113 (13.7 percent) had wheezing both before three years of age and at six years of age. The children who had wheezing before three years of age but not at the age of six had diminished airway function (length-adjusted maximal expiratory flow at functional residual capacity [$\dot{V}_{max}$FRC]) both before the age of one year and at the age of six years, were more likely than the other children to have mothers who smoked but not mothers with asthma, and did not have elevated serum IgE levels or skin-test reactivity. Children who started wheezing in early life and continued to wheeze at the age of six were more likely than the children who never wheezed to have mothers with a history of asthma ($P<0.001$), to have elevated serum IgE levels ($P<0.01$) and normal lung function in the first year of life, and to have elevated serum IgE levels ($P<0.001$) and diminished values for $\dot{V}_{max}$FRC ($P<0.01$) at six years of age.

Conclusions. The majority of infants with wheezing have transient conditions associated with diminished airway function at birth and do not have increased risks of asthma or allergies later in life. In a substantial minority of infants, however, wheezing episodes are probably related to a predisposition to asthma. (N Engl J Med 1995; 332:133-8.)

ALTHOUGH asthma may originate soon after birth,[1] the natural history of the disease is poorly understood. Many infants have episodes of wheezing associated with viral respiratory illnesses.[2] Neither the pathogenesis of these episodes nor their relation to asthma has been completely elucidated.[3] In older children and adults, the prevalence of asthma is strongly correlated with serum IgE levels and with skin-test reactivity to allergens,[4,5] but in one study no such relation was evident between early wheezing and serum IgE levels at birth.[6] Infants who have respiratory illnesses with wheezing in the first year of life have lower levels of lung function before any lower respiratory illness develops than do infants who do not have illnesses with wheezing.[7] This finding suggests that small airways predispose many infants to wheezing in association with common viral infections. However, it is possible that acute bronchial obstruction may have a variety of causes in early life, and a minority of infants with asthma may coexist with a larger group of infants with wheezing who have a more benign condition that is not mediated by IgE.

Older children with asthma have lower levels of lung function than children without asthma.[8] It is not known whether the reductions in lung function present before asthma develops contribute to asthma and con-

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tinue to be present later in life or whether reduced lung function in children with asthma is the consequence of chronic airway inflammation.

We studied the natural history of wheezing in the first six years of life. Specifically, we assessed the factors that affect wheezing before the age of three years and their relation to wheezing at six years of age.

METHODS

The children we studied were enrolled as newborns between May 1980 and October 1984 in the Tucson Children's Respiratory Study.[9] Their parents were patients of Group Health Medical Associates, a large health maintenance organization in Tucson, Arizona, and were contacted shortly after their children were born. Informed consent was obtained from the parents of 1246 newborns.

At the time of enrollment, the parents completed a questionnaire about their history of respiratory illness, smoking habits, and education. They were instructed to take their children to the pediatrician whenever the children had any of a defined set of signs and symptoms of lower respiratory tract illness (deep or "wet" chest cough, wheezing, hoarseness, stridor, or shortness of breath). The pediatricians obtained a detailed history at the time of such illnesses and recorded all relevant signs and symptoms (including wheezing on auscultation). Figure 1 shows the number of children for whom complete follow-up information on lower respiratory tract illnesses and complete data from questionnaires and tests were available.

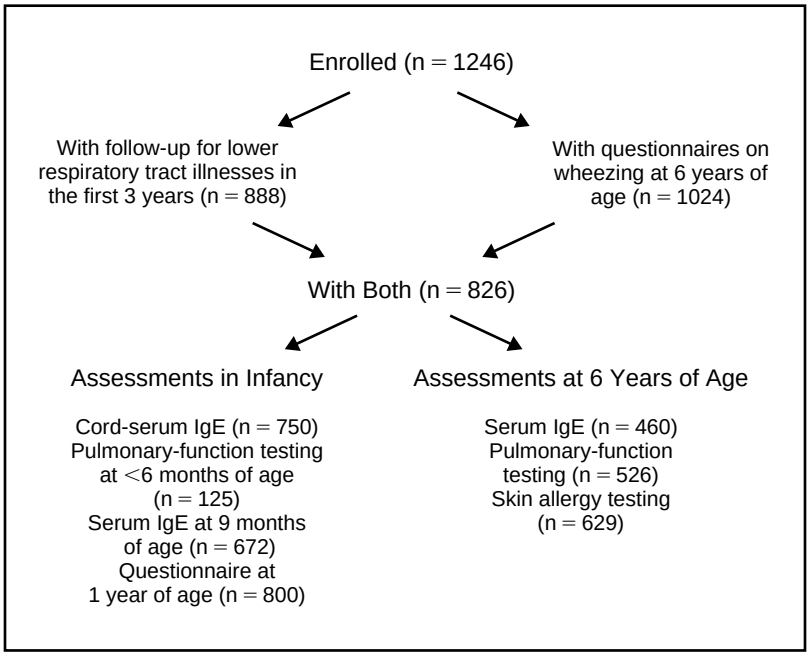

Figure 1. Number of Subjects Enrolled, Number with Complete Follow-up for Lower Respiratory Tract Illnesses in the First Three Years of Life, and Number for Whom Complete Data Were Available from Questionnaires and Tests.

A total of 826 children had follow-up data at three and six years of age and were included in the study.

Parents completed a questionnaire during their child's second year of life (mean[±SD] age, 1.6±0.4 years). Among other questions, parents were asked whether the child's "chest had ever sounded wheezy or whistling apart from colds" and how frequently the child wheezed. Parents were also asked whether their child ever had a runny nose apart from colds and whether a doctor had ever given the child a diagnosis of eczema. When the children reached a mean age of 6.3±0.9 years, parents again answered a questionnaire about the child's respiratory illnesses (referred to as the 6-year survey). In that questionnaire, current wheezing was defined as at least one episode of wheezing during the previous year.

During the first year of life, 176 infants underwent pulmonary-function testing. A detailed description of the selection criteria and the medical and social characteristics of these infants, as compared with those who were not tested, was reported earlier[7]; the frequency of a family history of asthma or allergies did not differ significantly between the infants who underwent pulmonary-function testing and those who were not tested. Of the 176 infants initially tested, 125 were tested before any lower respiratory tract illness occurred; complete follow-up data to the age of six years were available for these infants. Their mean age at the time of testing was 2.4±2.0 months.

Partial expiratory flow–volume curves were obtained by the chest-compression technique.[10] Briefly, informed consent was obtained from the parents, and the children were usually sedated with chloral hydrate (50 to 60 mg per kilogram of body weight). A plastic bag connected to a pressure reservoir was tightly wrapped around the child's chest and abdomen. A mask connected to a pneumotachygraph was sealed around the child's mouth and nose, and tidal flow–volume loops were displayed on a monitor. At end-tidal inspiration, the bag was rapidly inflated to a known pressure, compressing the child's chest and forcing air out of the lungs. The flow at the end-tidal expiration point was recorded from the forced flow–volume loops. This maneuver was repeated with increments in pressure of 5 to 10 cm of water. The maximal pressure applied to the thorax was the pressure at which no further increase in flow was obtained; this value — the maximal expiratory flow at functional residual capacity ($\dot{V}_{max}$FRC, expressed in milliliters per second) — was recorded and used in the analysis. $\dot{V}_{max}$FRC is believed to reflect the size of the intrapulmonary airways.[11]

At the time of the six-year survey, partial expiratory flow–volume curves were obtained with maneuvers to measure voluntary maximal expiratory flow.[12] Tidal flow–volume loops were recorded on a computer screen as described above. As the child approached end-tidal inspiration, he or she was encouraged to expel air forcefully, and a partial flow–volume curve was obtained. $\dot{V}_{max}$FRC was calculated from at least three acceptable expirations; the highest value obtained was used in our analyses.

Total serum IgE levels were measured with the paper radioimmunosorbent test (Pharmacia Diagnostics, Piscataway, N.J.) in samples obtained from cord blood, from blood obtained at a median age of 9.3 months (referred to as the 9-month sample), and from blood obtained at the time of the 6-year survey.

Skin allergy tests were performed concomitantly with lung-function testing at the time of the six-year survey with extracts of seven common aeroallergens in the Tucson area (Hollister–Stier Laboratories, Everett, Wash.). A child was considered to have atopy if he or she had at least one positive skin-test reaction (>2 mm of induration) to an aeroallergen. The aeroallergens tested were house-dust mix, alternaria, Bermuda grass, careless weed, mesquite, mulberry, and olive.

Statistical Analysis

Total serum IgE levels were expressed in international units per milliliter (1 IU per milliliter corresponded to 2.4 μg per liter). Log IgE values were adjusted for age according to standard regression techniques and expressed in terms of the median age (9.3 months) of the sample.

Values for $\dot{V}_{max}$FRC were logarithmically transformed for both age groups and adjusted for length or height. Results were standardized to the children's average length (57.4 cm) before the age of one year or height (110.3 cm) at the age of six.

Analysis of variance, Duncan's multiple-comparison test, chi-square tests, and logistic regression were used to compare means and proportions.[13] The 95 percent confidence intervals for odds ratios were calculated with standard algorithms.[14] Statistical significance was defined by a two-sided alpha level of 0.05.

This research was approved by the Human Subjects Committee at the University of Arizona. The parents signed separate consent forms for the infants' initial enrollment and for the other studies described in this report.

RESULTS

When the 826 children included in this study were compared with the 420 who were excluded because of incomplete data, the frequency of a family history of asthma and the distribution of ethnic backgrounds were similar. However, the children with complete data tended to belong to families with a higher socioeconomic status and a lower prevalence of maternal smoking (data not shown).

Table 1. Adjusted Odds Ratios for Transient Early Wheezing, Late-Onset Wheezing, and Persistent Wheezing, According to Risk Factors Present at One Year of Age, and Prevalence of Risk Factors.*

Risk Factor	No Wheezing (N = 403)	Transient Early Wheezing (N = 147)	Late-Onset Wheezing (N = 112)	Persistent Wheezing (N = 100)
Eczema				
Odds ratio (95% CI)	1.0	1.3 (0.7–2.5)	0.7 (0.3–1.6)	2.4 (1.3–4.6)
Prevalence (%)	7.7	10.2	6.3	18.0
Rhinitis apart from colds				
Odds ratio (95% CI)	1.0	1.1 (0.7–1.7)	1.7 (1.1–2.7)	2.0 (1.2–3.2)
Prevalence (%)	24.8	27.2	35.7	42.0
Maternal asthma				
Odds ratio (95% CI)	1.0	1.6 (0.8–3.2)	2.8 (1.4–5.5)	4.1 (2.1–7.9)
Prevalence (%)	6.7	10.2	16.1	22.0
Hispanic ethnic background				
Odds ratio (95% CI)	1.0	1.5 (0.9–2.7)	1.7 (0.9–3.1)	3.0 (1.6–5.5)
Prevalence (%)	10.7	13.6	14.3	22.0
Male sex				
Odds ratio (95% CI)	1.0	1.0 (0.7–1.5)	2.1 (1.3–3.4)	1.9 (1.2–3.0)
Prevalence (%)	42.7	44.2	61.6	61.0
Maternal smoking				
Odds ratio (95% CI)	1.0	2.2 (1.3–3.7)	1.6 (0.9–2.9)	2.3 (1.2–4.4)
Prevalence (%)	11.4	21.2	17.0	21.0

*Three different logistic regressions were performed comparing each of the three groups with wheezing with the children who never had wheezing. Subjects without a given risk factor were assigned a value of 0 and those with the risk factor a value of 1. Sixty-four patients had missing data for explanatory variables and were excluded from this analysis (22 who never had wheezing, 17 with transient early wheezing, 12 with late-onset wheezing, and 13 with persistent wheezing). The odds ratios have been adjusted in the logistic-regression model for all the other risk factors listed. CI denotes confidence interval.

Children were assigned to four categories according to their history of wheezing: those who had no recorded lower respiratory tract illness with wheezing during the first three years of life and had no wheezing at six years of age (children who had never had wheezing); those with at least one lower respiratory tract illness with wheezing during the first three years of life but no wheezing at six years of age (those with transient early wheezing); those who had no lower respiratory tract illness with wheezing during the first three years of life but who had wheezing at six years of age (those with wheezing of late onset); and those who had at least one lower respiratory tract illness with wheezing in the first three years of life and had wheezing at six years of age (those with persistent wheezing). A total of 425 children (51.5 percent) were classified as never having wheezed, 164 (19.9 percent) as having had transient early wheezing, 124 (15.0 percent) as having wheezing of late onset, and 113 (13.7 percent) as having persistent wheezing.

Of 277 children who had wheezing before the age of three, 164 (59.2 percent) had not wheezed during the previous year when they were evaluated at six years of age. Maternal asthma, maternal smoking, rhinitis apart from colds, eczema during the first year of life, male sex, and Hispanic ethnic background were all independently associated with persistent wheezing. Of the variables we considered, only maternal smoking was significantly associated with transient early wheezing (Table 1). Children with wheezing of late onset were significantly more likely than those who had never wheezed to have mothers with asthma, to be male, and to have had rhinitis in the first year of life. Those with persistent wheezing were significantly more likely than those without wheezing to have mothers with asthma ($P<0.001$). The results in each category of wheezing were not changed by adjustment for the parents' level of education.

When compared with the children with transient early wheezing, those with persistent wheezing were more than twice as likely to have wheezed often or very often (odds ratio, 2.3; 95 percent confidence interval, 1.4 to 3.8; $P=0.001$) and were more likely to have had wheezing without colds during infancy (odds ratio, 1.8; 95 percent confidence interval, 1.0 to 3.4; $P=0.05$). At six years of age, 22.5 percent of children with late-onset wheezing had been given a diagnosis of asthma, as compared with 46.0 percent of children with persistent wheezing ($P<0.001$); 25.0 percent of children with late-onset wheezing had been given a diagnosis of bronchitis without asthma, as had 22.1 percent of those with persistent wheezing ($P=0.7$).

Children with transient early wheezing had significantly lower length-adjusted values for $\dot{V}_{max}$FRC in infancy than all the other groups (Table 2). The children with persistent wheezing or wheezing of late onset had $\dot{V}_{max}$FRC values that were not significantly different from those of the children who had never had wheezing. At the age of six, the children with transient early wheezing still had significantly lower height-adjusted $\dot{V}_{max}$FRC values than those who had never wheezed, and the children with persistent wheezing had the lowest levels of lung function of all the groups. As compared with the children who had never wheezed, those with persistent wheezing were significantly more likely to have diminished values for $\dot{V}_{max}$FRC ($P<0.01$). Children with late-onset wheezing had $\dot{V}_{max}$FRC levels that were not significantly different from those of the children who had never wheezed.

Cord-serum IgE levels were unrelated to a later history of wheezing (Fig. 2). Only children with persistent

Table 2. Maximal Expiratory Flow at Functional Residual Capacity ($\dot{V}_{max}$FRC) during the First Year of Life and at Six Years of Age, According to History of Wheezing.*

Age	No Wheezing		Transient Early Wheezing		Late-Onset Wheezing		Persistent Wheezing		F	P Value
	no.	$\dot{V}_{max}$FRC	no.	$\dot{V}_{max}$FRC	no.	$\dot{V}_{max}$FRC	no.	$\dot{V}_{max}$FRC		
		ml/sec		*ml/sec*		*ml/sec*		*ml/sec*		
<1 year	67	123.3 (110.0–138.0)	21	70.6 (52.2–93.8)†	21	107.1 (87.5–129.6)	16	104.6 (73.6–144.5)	5.95	<0.001
6 years	260	1262.1 (1217.4–1308.1)	104	1097.7 (1034.9–1163.5)‡	81	1174.9 (1111.1–1241.1)	81	1069.7 (906.9–1146.5)‡	9.60	<0.001

*A total of 125 children underwent pulmonary-function testing during the first year of life, and 526 were tested at six years of age. Values for $\dot{V}_{max}$FRC are geometric means (95 percent confidence intervals). The F-test and associated P values indicate significant differences in lung function between the four groups.

†P<0.01 for the comparison with the children who never wheezed and P<0.05 for the comparisons with the children with late-onset wheezing and persistent wheezing, by Duncan's multiple-comparison test.

‡P<0.01 for the comparison with the children who never wheezed, by Duncan's multiple-comparison test.

wheezing had significantly higher IgE levels at nine months of age than those who had never wheezed (P<0.01). The geometric mean IgE levels were 3.4 IU per milliliter (95 percent confidence interval, 3.0 to 3.9) for children who had never wheezed, 3.7 (95 percent confidence interval, 3.1 to 4.4) for those with transient early wheezing, 3.8 (95 percent confidence interval, 2.9 to 5.0) for those with wheezing of late onset, and 5.2 (95 percent confidence interval, 3.8 to 7.2) for those with persistent wheezing. The risk of belonging to any of the three groups with wheezing was evaluated according to the level of IgE at nine months of age (Fig. 2). A direct relation between IgE levels and wheezing was seen only for children with persistent wheezing (P = 0.02).

Children with transient early wheezing and those

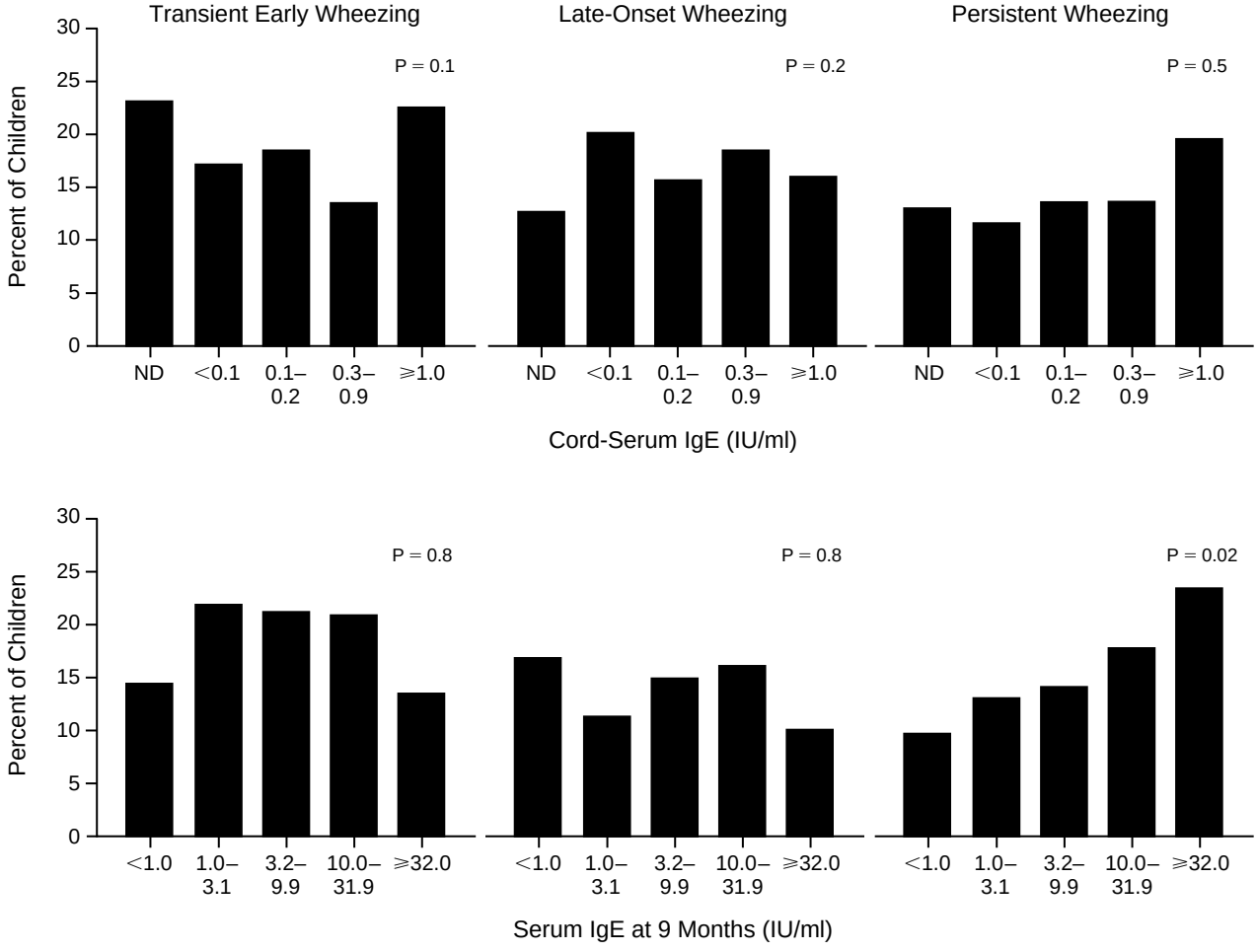

Figure 2. Proportion of Subjects Who Had Transient Early Wheezing, Wheezing of Late Onset, and Persistent Wheezing, According to Cord-Serum IgE Levels and Serum IgE Levels at Nine Months of Age.

The categories of wheezing are defined in the text. The numbers of children with the various IgE levels were as follows: for cord serum, not detectable (ND), 290; <0.1 IU per milliliter, 296; 0.1 to 0.2 IU per milliliter, 117; 0.3 to 0.9 IU per milliliter, 20; and ≥1.0 IU per milliliter, 10; for serum at nine months, <1.0 IU per milliliter, 83; 1.0 to 3.1 IU per milliliter, 230; 3.2 to 9.9 IU per milliliter, 209; 10.0 to 31.9 IU per milliliter, 123; and ≥32.0 IU per milliliter, 27. P values for trend within the groups were determined by the chi-square test.

Table 3. Total Serum IgE Levels and Prevalence of Positive Skin Tests for Reactivity to Aeroallergens in Children Six Years Old, According to History of Wheezing.*

CATEGORY	SERUM IGE†		POSITIVE SKIN TEST	
	NO. TESTED	MEAN (95% CI)	NO. TESTED	PREVALENCE
		IU/ml		%
No wheezing	222	28.1 (22.4–35.3)	317	33.8
Transient early wheezing	95	31.0 (22.3–43.1)	125	38.4
Late-onset wheezing	68	42.1 (26.6–66.0)	97	55.7‡
Persistent wheezing	75	65.6 (45.3–94.4)§	90	51.1¶
		$F = 4.94$ $P = 0.002$		$\chi^2 = 19.5$ $P < 0.001$

*Of the 826 children, 629 underwent skin testing for reactivity to aeroallergens and 460 had measurements of serum IgE at six years of age. The F-test and the chi-square test (and the corresponding P values) indicate significant differences in serum IgE levels and the prevalence of positive skin tests, respectively, in association with the differences in patterns of wheezing.

†To convert values for IgE to micrograms per liter, multiply by 2.4. CI denotes confidence interval.

‡$P < 0.001$ for the comparison with the children who never wheezed.

§$P < 0.01$ for the comparisons with the children who never wheezed and those with transient early wheezing, by Duncan's multiple-comparison test.

¶$P = 0.003$ for the comparison with the children who never wheezed.

who had never wheezed had similar serum IgE levels and a similar prevalence of atopy at the age of six years (Table 3). Those with persistent wheezing had significantly higher levels of IgE than those who had never wheezed ($P < 0.01$). Children with late-onset wheezing did not have significantly elevated serum IgE levels as compared with those who had never wheezed. Atopy was significantly more prevalent in both groups of children with wheezing at the age of six than in the group that had never wheezed. After adjustment for skin-test reactivity with multiple regression analysis, the children with persistent wheezing had significantly higher levels of IgE at the age of six years than the children with late-onset wheezing ($P = 0.03$).

DISCUSSION

We found that wheezing in the first three years of life had a rather benign prognosis. Although one third of all children three years of age or younger had lower respiratory tract illnesses with wheezing, almost 60 percent of these children had stopped wheezing by the age of six years. Children with transient early wheezing were distinguished from the other groups who had wheezing by their lower levels of lung function, as indicated by their values for $\dot{V}_{max}FRC$. As described earlier,[15] this diminished lung function was evident shortly after birth and before any lower respiratory tract illness had occurred. One possibility is that this finding reflected congenitally smaller airways and predisposed these infants to wheezing in early life. We found that children with transient early wheezing still had reduced values for $\dot{V}_{max}FRC$ at six years of age, as compared with their peers, although the children were no longer symptomatic. As their airways grow in absolute size with age, these children may become less apt to have wheezing during viral infections.

Smoking by a child's mother was also a risk factor for transient early wheezing. The infants of mothers who smoked during pregnancy had significantly lower values for $\dot{V}_{max}FRC$[16] than the infants of mothers who did not smoke. The association between maternal smoking and transient early wheezing may be mediated, at least in part, by smaller airways in the children of women who smoke.

Children with persistent wheezing had initial values for $\dot{V}_{max}FRC$ that were similar to those of the children who never wheezed but were almost 50 percent higher than those of children with transient early wheezing. Factors other than small airways may cause early wheezing in infants in whom episodes of wheezing persist up to the age of six years. Children with persistent wheezing had more frequent symptoms during the first year of life than those with transient early wheezing. Most of the risk factors for persistent wheezing (eczema, rhinitis apart from colds, and maternal asthma, among others) were not associated with increased risk among the children with transient early wheezing. Maternal smoking was the only risk factor common to both groups, suggesting that exposure to tobacco smoke may have effects other than those on airway growth in utero.[17]

There was a significant, direct relation between the risk of persistent wheezing and the serum IgE level at nine months of age. This relation was very similar to that reported between serum IgE levels and asthma in older children and adults,[4,5] and it contrasts with the lack of association between transient early wheezing or late-onset wheezing and serum IgE levels at nine months. No relation was found between the risk of persistent wheezing at six years of age and cord-serum IgE levels, suggesting that some form of IgE-mediated sensitization may occur during the first year of life in children with persistent wheezing. Such sensitization may contribute to early wheezing, in much the same way as it is thought to predispose older children to asthma.

We could not determine the nature of this allergic sensitization on the basis of our data. It is clear, however, that by the age of six years, children with persistent wheezing were as frequently sensitized to common aeroallergens as those with wheezing of late onset. One hypothesis is that children with persistent wheezing may have been sensitized to these antigens during the first year of life, whereas children with late-onset wheezing were not. An alternative hypothesis is that children with persistent wheezing are predisposed to produce large quantities of IgE in response to a variety of antigens and that this enhanced IgE reactivity may be expressed in response to different allergens at different ages. Further studies of allergic sensitization in early life are indicated.[18]

Most of the children with lower respiratory tract illnesses in our study were infected with respiratory syncytial virus or parainfluenza viruses.[2] Welliver et al. found a higher prevalence of specific IgE against respiratory syncytial virus[19] and parainfluenza virus[20] in the nasal secretions of infants with wheezing who had these infections than in the secretions of infants with these infections who did not have wheezing. In infants with confirmed respiratory syncytial virus infections in the first six months of life, the frequency of persistent

wheezing up to seven or eight years of age was directly related to the level of respiratory syncytial virus–specific IgE in their nasopharyngeal secretions during the initial episode.[21] The children who had persistent wheezing in our study may have been more prone than the others to produce virus-specific IgE in early life. This factor could explain their higher levels of IgE at a mean age of nine months.

Children with persistent wheezing had significantly reduced lung function, as indicated by $\dot{V}_{max}$FRC values, at the age of six years. This deterioration in airway function is consistent with the substantial deficits in lung function reported in older children with asthma.[8] Our data suggest that among children with persistent wheezing these deficits are not caused by poorer initial lung function but, rather, may reflect the effects of the chronic disease process on the bronchi. We do not know whether the deficits reflect irreversible damage to the airways or a reversible increase in airway muscle tone. Recent reports suggest, however, that in people with asthma, lung volume and maximal flow grow at similar, normal rates from 9 to 17 years of age and that any irreversible damage may have already occurred by 9 years of age.[22]

Our data did not permit us to elucidate the mechanisms of the deficits in lung function in children with persistent wheezing. We doubt, however, that they result from direct, nonspecific injuries produced by viral infections in early life. If this were the case, similar deficits should have been seen among the children with transient early wheezing. It is possible that in children with persistent wheezing, much as in older patients with asthma, chronically elevated serum IgE levels may be associated with chronic airway inflammation,[23] persistent bronchial hyperresponsiveness,[5] and abnormalities in the development of airway function.[24] Such associations could also help to explain why children with late-onset wheezing, whose serum IgE levels were not elevated at nine months of age and were only mildly elevated at six years, had lung function at the age of six that was within the normal range.

In summary, our findings suggest that most infants who wheeze have transient conditions associated with diminished airway function and have no increased risk of asthma or allergies later in life. In a minority of infants, early wheezing episodes are probably related to a predisposition to asthma. Such children already have elevated serum IgE levels during the first months of life and have substantial deficits in lung function by the age of six years.

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Wheezing and bronchial hyper-responsiveness in early childhood as predictors of newly diagnosed asthma in early adulthood: a longitudinal birth-cohort study

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Summary

Background **Incidence of asthma increases during early adulthood. We aimed to estimate the contributions of sex and early life factors to asthma diagnosed in young adults.**

Methods **1246 healthy newborn babies were enrolled in the Tucson Children's Respiratory Study. Parental characteristics, early-life wheezing phenotypes, airway function, and bronchial hyper-responsiveness to cold dry air and sensitisation to *Alternaria alternata* were determined before age 6 years. Physician-diagnosed asthma, both chronic and newly diagnosed, and airway function were recorded at age 22 years.**

Findings **Of 1246 babies enrolled, 849 had follow-up data at 22 years. Average incidence of asthma at age 16–22 years was 12·6 per thousand person-years. 49 (27%) of all 181 cases of active asthma at 22 years were newly diagnosed, of which 35 (71%) were women. Asthma remittance by 22 years was higher in men than in women (multinomial odds ratio [M-OR] 2·0, 95% CI 1·2–3·2, p=0·008). Age at diagnosis was linearly associated with the ratio of forced expiratory volume at 1 s to forced vital capacity at age 22 years. Factors independently associated with chronic asthma at 22 years included onset at 6 years (7·4, 3·9–14·0) and persistent wheezing (14·0, 6·8–28·0) in early life, sensitisation to *A alternata* (3·6, 2·1–6·4), low airway function at age 6 years (2·1, 1·1–3·9), and bronchial hyper-responsiveness at 6 years (4·5, 1·9–10·0). Bronchial hyper-responsiveness (6·9, 2·3–21·0), low airway function at 6 years (2·8, 1·1–6·9), and late-onset (4·6, 1·7–12·0) and persistent wheezing (4·0, 1·2–14·0) predicted newly diagnosed asthma at age 22 years.**

Interpretation **Asthma with onset in early adulthood has its origins in early childhood.**

Funding **National Heart Lung and Blood Institute.**

Introduction

Several lines of evidence indicate that most people diagnosed with asthma in the first two decades of life had recurrent episodes of wheezing in early childhood,[1] suggesting that the disease process might have started years before diagnosis. Prospective data from the 1958 British cohort[2] indicated an upsurge in incident cases of asthma and wheezing in early adulthood. This second wave of newly diagnosed disease has not been extensively studied but constitutes a high proportion of asthma in young adults and contributes to respiratory morbidity in this age group, especially in women.[3] Whether factors in early life contribute to the risk of this second wave of asthma, as they do for asthma developing during the school years, is unknown. Strachan and co-workers[2] reported that pre-existing allergic rhinitis was an important risk factor for new-onset asthma in early adult life; Guerra and colleagues[4] confirmed this finding and suggested that allergy-related factors might play a part. Whether respiratory events and changes in airway and immune reactivity before age 6 years affect the incidence and prevalence of asthma in early adulthood needs to be assessed.

Children who have lower respiratory tract illnesses in early life are at increased risk of wheezing and asthma.[5,6] In a longitudinal study of unselected children,[1] we showed that those who are wheezing at age 6 years are at increased risk of subsequent asthma up to the age of 16 years, whereas those with transient early wheezing (ie, those who wheeze with lower respiratory tract illnesses but do not report wheezing at age 6 years) are not. What the relation is between these early wheezing phenotypes and new-onset asthma in early adulthood is unknown.

Bronchial hyper-responsiveness, a central characteristic of asthma irrespective of age at onset,[7] is an abnormal bronchoconstrictive response to various stimuli. We previously showed in this same longitudinal cohort that non-asthmatic children with bronchial hyper-responsiveness at age 6 years were at increased risk of asthma by 11 years, but the association was not independent of allergic sensitisation and mild wheezing at 6 years.[8]

We aimed to determine whether potential risk factors for asthma measured during the preschool years predict prevalence, incidence, and remission of physician-diagnosed asthma and asthma-like symptoms in early adulthood.

Methods

Study design

Healthy infants were enrolled at birth in the Tucson Children's Respiratory Study in Tucson, AZ, USA,

	2–16 years	22 years
No asthma	–	–
Inactive	+	–
Newly diagnosed	–	+
Chronic	+	+

Table 1: **Definitions of asthma at 22 years on the basis of physician diagnosed asthma and current symptoms**

between 1980 and 1984.[9] Parents were contacted shortly after their children were born and completed a questionnaire describing their ethnicity, history of physician-diagnosed asthma, years of education, and current smoking habits. Informed consent was obtained from the parents for their children, or by the enrollees themselves if appropriate, and the Institutional Review Board of the University of Arizona approved the study.

Data collection

Parents were instructed at enrolment to bring their child to collaborating paediatricians at the first signs or symptoms of a lower respiratory illness before age 3 years.[10] Wheezing was identified by the physician. Physician-diagnosed asthma and current wheeze in the previous year were assessed from questionnaires completed for the children by their parents or adult carers at ages 2, 3, 6, 8, 11, 13, and 16 years. If a physician diagnosis of asthma with active symptoms was ever reported on a questionnaire, the participant was classified as having asthma by age 16 years.

Skin-prick tests for seven local aeroallergens (Bermuda grass, *Alternaria alternata*, careless weed, house-dust mix, and mesquite, mulberry, and olive-tree pollens) were done at age 6 years as previously described.[11] Tests were read at 20 min and the sum of the largest wheal diameter plus the perpendicular diameter recorded. We classified wheals greater than or equal to 3 mm, after subtracting the negative control, as positive.

	Adult data	No adult data	p value
Male	410/858 (48%)	203/388 (52%)	0·14
Ethnicity*	554/858 (65%)	180/388 (46%)	<0·0001
Early wheezing phenotypes			
Never	355/687 (52%)	70/139 (50%)	
Transient	138/687 (20%)	26/139 (19%)	
Late	108/687 (16%)	16/139 (12%)	
Persistent	86/687 (13%)	27/139 (19%)	0·1†
Any skin test‡	260/667 (39%)	34/95 (36%)	0·6
Alternaria skin test‡	114/666 (17%)	19/95 (20%)	0·5
Parental characteristics			
Mother asthmatic	90/845 (11%)	37/310 (12%)	0·5
Father asthmatic	98/812 (12%)	34/282 (12%)	0·9
Mother smoker	128/858 (15%)	92/385 (24%)	<0·001
Father smoker	235/846 (28%)	150/380 (40%)	<0·001
Mother educated >12 years	640/857 (75%)	207/384 (54%)	<0·001
Father educated >12 years	644/842 (77%)	212/375 (57%)	<0·001

Data are number (%). *Two non-Hispanic white parents. †3 df. ‡At age 6 years.

Table 2: **Characteristics of participants with data at age 22 years (n=858) and those without (n=388)**

Participants did a cold-air challenge at a mean age of 6·1 years (SD 0·5).[8] Children who were actively wheezing, who had used drugs to help their breathing in the past 48 h, who had had a lower respiratory illness during the previous 6 weeks, or who had had upper-respiratory-tract infection during the previous 3 weeks were rescheduled for testing. Those who required continuous treatment or could not be rescheduled were not tested. Baseline maximum expiratory flow at functional residual capacity ($\dot{V}_{max}FRC$) measured in millilitres per second was recorded from the best of three voluntary partial expiratory manoeuvres as previously described.[8] The children then breathed CO_2-enriched cold (–20°C) dry air for 6 min and the mean of the first two values of $\dot{V}_{max}FRC$ measured within 5 min was taken as the postchallenge value. Bronchial responsiveness was calculated as percentage fall in $\dot{V}_{max}FRC$. Cold-air bronchial hyper-responsiveness was defined as a drop greater than 41·1%, the 90th percentile of decline for reference children (those with negative skin-tests, classified as never wheezing, who had not been diagnosed with asthma by age 6 years).[8]

We included previously described early wheezing phenotypes as risk factors:[5] persistent wheezing (wheeze developed during lower respiratory tract infection before age 3 years and lasted to 6 years), late-onset wheezing (no lower respiratory tract infections with wheezing before age 3 years but wheezing by age 6 years), transient early wheezing (wheezing during infection in early life but not wheezing at 6 years), and never wheezing (no lower respiratory tract infections with wheezing and no wheezing at 6 years).

Data for the occurrence of respiratory symptoms during the previous year were obtained from questionnaires completed at the in-depth assessment at age 22 years, and, if no data were available at that age, data from questionnaires at ages 24 years or 18 years were used. Current wheeze was defined as having had at least one self-reported episode during the previous year. Shortness of breath with wheeze was defined as infrequent (one to three), frequent (four or more), or any (infrequent and frequent combined) episodes during the previous year. Current asthma at age 22 years was defined as having ever had a physician diagnosis with active symptoms (attacks, episodes, or wheeze) during the previous year. Current asthma at 22 years was subdivided into four categories (table 1). Those with current asthma were further subdivided into those who had taken any prescription drugs for asthma or wheeze in the past year and those who had not. Current cigarette smoking was determined from questionnaire responses.

	Before (Z scores)			After (Z scores)		Response* (Z scores)	
	n	Mean (SE)	p	Mean (SE)	p	Mean (SE)	p
No asthma	317	0·10 (0·05)	..	0·09 (0·05)	..	−0·08 (0·05)	..
Inactive	44	0·09 (0·15)	0·9	0·16 (0·14)	0·6	−0·07 (0·15)	0·9
Newly diagnosed	24	−0·49 (0·20)	0·005	−0·47 (0·19)	0·009	0·21 (0·30)	0·4†
Chronic	69	−0·37 (0·15)	0·004†	−0·33 (0·15)	0·009†	0·32 (0·15)	0·016†

Each lung function outcome was adjusted for sex in a linear regression and the standardised residuals from the regression (Z scores) were saved and used as the outcome measures for this table. A Z score of 1 represents one standard deviation from the group mean of zero. p values computed with linear regression for each outcome with the no asthma group as the reference group. *Bronchodilator response calculated with FEV_1 (mL) as 200x([after–before]/[after+before]). †Levene's test for equality of variances was significant for this comparison and so we used an unequal variances *t* test to compute the p value with reference to the no asthma group.

Table 3: **Prebronchodilator and postbronchodilator FEV1/FVC ratio and response to bronchodilator for asthma groups at age 22 years**

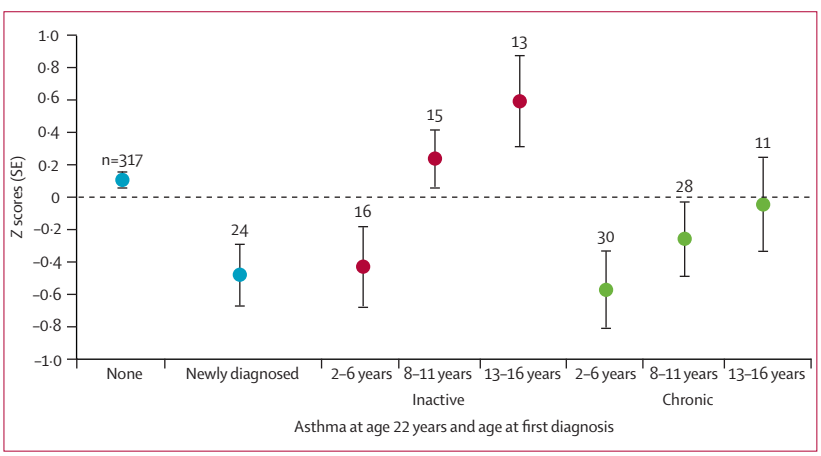

Figure: **FEV_1/FVC ratio and asthma at age 22 years by age at first asthma diagnosis**
FEV_1/FVC ratio was adjusted for sex in a linear regression and the standardised residuals from the regression (Z scores with SE) were saved and used as the outcome measure for this figure (a Z score of 1 represents 1 SD from the group mean of zero). Age at first diagnosis was divided into three groups on the basis of when the diagnosis was first reported. Age at diagnosis was significantly and linearly related to the FEV_1/FVC ratio (p=0·009) in people with inactive and chronic asthma at age 22 years, after adjusting for asthma status and sex.

Allergy skin-prick tests were done at age 22 years (n=462) for 17 local aeroallergens including: house-dust mix, cat hair, cat pelt, dog, cockroach, *Dermatophagoides farinae*, *Penicillium notatum*, *Aspergillus fumigatus*, *Hormodendrum cladosporioides*, *A alternata* (the main asthma-associated allergen in the Tucson area[11]), and the pollens of Bermuda grass, olive tree, careless weed, mesquite tree, mulberry tree, and ragweed. Methods were the same as for testing at age 6 years.

Spirometry was done at age 22 years (n=456) with a portable Schiller Spirovit SP-1 (Schiller AG, Baar, Switzerland).[1] Systems were calibrated with a Jones flow-volume calibrator (Model FVC-3000; Jones Medical Instrumentation Company, Oakbrook, IL, USA). No participants had used a bronchodilator within 6 h of testing. Study nurses recorded height, weight, and age at time of testing. Subsequent to baseline measurements, a fixed dose of two puffs of salbutamol (180 µg) was given from a metred-dose inhaler and aerochamber holding device (Monaghan Medical Corp, Plattsburgh, NY, USA) and postbronchodilator spirometry obtained after 15 min. Spirometry indices included forced vital capacity (FVC, mL) and forced expiratory volume in 1 s (FEV_1, mL). Response to bronchodilator was calculated as 200×([after–before]/[after+before]).

Statistical analysis

Proportions were compared with χ^2 analysis or Fisher's exact test as appropriate; odds ratios (ORs) were calculated with logistic regression. Multinomial logistic regression was used to estimate multinomial odds ratios (M-OR, also known as relative-risk ratios) for categorical outcomes. To allow for all participating patients to be included in the regression models, dummy missing categories were used when predictor variables had missing information. Full regression models included all variables, best-fitting models included those variables with p<0·1 in the full model. Attributable risk was calculated as ([OR–1]÷OR)×proportion of participants who had the risk factor. Significance was defined as two-tailed p-values less than 0·05. Statistical analyses were done with SPSS for Windows (v 15.0) and STATA (v 10.0).

Role of the funding source

The sponsor had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

1246 children were enrolled. 858 had data at 22 years; mean age at final data collection was 21·7 years (SD 1·2)—735 collected at 22 years, 77 at 18 years, and 46 at 24 years. Of these 858, 835 completed questionnaires at 2 (mean age 1·6 years, SD 0·3), 769 at 3 (2·9, 0·5), 840 at 6 (6·2, 0·9), 727 at 8 (8·6, 0·7), 831 at 11 (10·9, 0·6), 646 at 13 (13·5, 0·6), and 712 at 16 (16·6, 0·6) years. Individuals who had information for asthma and respiratory symptoms at age 22 years were more likely to have non-smoking, non-Hispanic white parents with more years of education than those who did not have information (table 2). There were no differences in the proportion of men, early wheezing phenotypes, atopy or *Alternaria* sensitisation at age 6 years, or parental history of asthma between the two groups.

The number of participants who had complete data for all parts of each question about asthma, wheeze, shortness of breath, and smoking varied; those with incomplete data were excluded from analysis. Of 849 participants with data at age 22 years, 255 (30%) reported ever receiving a physician diagnosis of asthma. 22% (181) reported active asthma, and 19% (163) reported wheeze without a diagnosis of asthma. 163 (19%) of 850 reported shortness of breath with wheeze during the previous year and 61 (7%) had these symptoms frequently. 224 (26%) of 851 participants reported currently smoking cigarettes at 22 years.

Parental asthma and cold-air bronchial hyper-responsiveness at age 6 years, *Alternaria* skin-test reactivity and low V'maxFRC were all strongly associated with an increased risk for asthma and shortness of breath at 22 years (webtable 1). Ethnicity (data not shown) and eczema at age 2 years were unrelated to asthma symptoms at 22 years (webtable 2). People with persistent and late-onset wheeze in early childhood were more likely to have current asthma and shortness of breath with wheeze at age 22 years than were those who had no reporting of wheezing by 6 years (webtable 1). Smoking at 22 years was associated with increased reporting of asthma and wheeze at that age. When multinomial logistic regression was done with current asthma and wheeze only as the outcomes compared with the no asthma and no wheeze group, late and persistent wheezing, parental asthma, cold-air bronchial hyper-responsiveness at age 6 years, sensitisation to *A alternata*, and low V'maxFRC were all positively and independently associated with current asthma and shortness of breath with wheeze at age 22 years (webtable 2).

Of 849 individuals with information about asthma at age 22 years, 496 (58%) completed all seven questionnaires administered between age 2 years and 16 years, 335 (39%) completed four, five, or six questionnaires, and 18 (2%) completed up to three questionnaires. On average, participants completed six questionnaires. By age 16 years, 206 (24%) had reported a diagnosis of asthma at least once. Of 643 individuals who never reported physician diagnosed asthma by age 16 years, 412 (64%) had at least one report of wheezing at age 2–16 years.

49 patients had newly diagnosed asthma at age 22 years, average yearly incidence was 12·6 per thousand person-years. 74 had inactive asthma, 132 chronic asthma, and 594 no asthma. When compared with no asthma, newly diagnosed and chronic asthma were strongly associated with current shortness of breath and cough (webtable 3). All three asthma categories were associated with concurrent skin-test positivity.

To assess asthma severity, newly diagnosed and chronic asthma were further divided according to whether any prescription drugs were used to treat asthma or wheezing during the previous year (webtable 4). For newly diagnosed asthma, there was no difference in shortness of breath with wheezing, cough, or skin-test positivity between those using drugs and those who did not. By contrast, participants with chronic asthma who were using drugs were more likely to have shortness of breath with wheeze than those who did not (53 [76%] of 70 *vs* 25 [40%] of 62, respectively, p<0·0001). Prevalence of cough and skin test positivity was the same in both groups.

Similar values for prebronchodilator and post-bronchodilator ratio of FEV_1 to FVC and response to bronchodilator were recorded for the inactive asthma and no asthma groups at age 22 years (table 3). In contrast, the prebronchodilator and postbronchodilator FEV_1/FVC ratio was significantly lower in both newly diagnosed and chronic asthma than in no asthma. The response to bronchodilator was significantly higher in chronic asthma, but not in newly diagnosed asthma, than in no asthma. When current asthma was further subdivided by prescription drugs used for asthma during the previous year, different patterns were recorded for the newly diagnosed and chronic groups (webtable 5). Whereas patients with newly diagnosed asthma have a low FEV_1/FVC ratio irrespective of drug use, only patients with chronic asthma using drug treatment had a low FEV_1/FVC ratio compared with those not on drugs.

Participants with asthma at age 22 years were subdivided into three categories prospectively defined on the basis of age at diagnosis: 2–6 years, 8–11 years, and 13–16 years. There was no significant difference at age at

	No asthma	Inactive	p	Newly diagnosed	p	Chronic	p
Sex							
Male (404)	271	46 (15%)	..	14 (5%)	..	73 (21%)	..
Female (445)	323	28 (8%)	0·008	35 (10%)	0·023	59 (15%)	0·045
Parental asthma							
Neither (622)	468	51 (10%)	..	30 (6%)	..	73 (14%)	..
Either (179)	93	20 (18%)	0·018	17 (16%)	0·001	49 (35%)	<0·0001
Parental smoking							
No (565)	395	54 (12%)	..	31 (7%)	..	85 (18%)	..
Yes (273)	194	18 (9%)	0·18	17 (8%)	0·7	44 (19%)	0·8
Physician diagnosed eczema by 2 years							
No (696)	502	51 (9%)	..	43 (8%)	..	100 (17%)	..
Yes (79)	40	16 (29%)	<0·0001	4 (9%)	0·8	19 (32%)	0·004
Early wheezing phenotype							
Never (354)	297	19 (6%)	..	13 (4%)	..	25 (8%)	..
Transient (135)	99	11 (10%)	0·16	10 (9%)	0·055	15 (13%)	0·090
Late onset (107)	47	18 (28%)	<0·0001	8 (15%)	0·004	34 (42%)	<0·0001
Persistent (86)	27	17 (39%)	<0·0001	4 (13%)	0·044	38 (59%)	<0·0001
***Alternaria* skin-test positive at 6 years**							
No (546)	399	47 (11%)	..	31 (7%)	..	69 (15%)	..
Yes (113)	51	15 (23%)	0·006	3 (6%)	0·7	44 (46%)	<0·0001
CA-BHR at 6 years							
No (330)	262	25 (9%)	..	11 (4%)	..	32 (11%)	..
Yes (58)	29	7 (19%)	0·048	7 (19%)	0·001	15 (34%)	<0·0001
V'maxFRC quartiles at 6 years							
High (132)	106	10 (9%)	..	7 (6%)	..	9 (8%)	..
Med–high (132)	91	13 (13%)	0·4	3 (3%)	0·3	25 (22%)	0·005
Med–low (132)	91	16 (15%)	0·15	6 (6%)	0·9	19 (17%)	0·036
Low (132)	75	13 (15%)	0·17	10 (12%)	0·17	34 (31%)	<0·0001
Smoking at 22 years							
No (625)	439	62 (12%)	..	30 (6%)	..	94 (18%)	..
Yes (224)	155	12 (7%)	0·068	19 (11%)	0·058	38 (20%)	0·5

Data are number (%). Percentages for each asthma group were calculated with respect to the no asthma group after excluding the other two asthma groups. Significance (p values) for the association between each individual risk factor and the asthma groups were estimated using multinomial logistic regression with respect to the no asthma group. CA-BHR=bronchial hyper-responsiveness to cold air challenge at age 6 years.

Table 4: **Proportion of participants with early-life risk factors and current smoking by asthma group at age 22 years**

See Online for webtables 1–5

	Inactive		Newly diagnosed		Chronic	
	M-OR† (95% CI)	p	M-OR (95% CI)	p	M-OR (95% CI)	p
Parental asthma	2·0 (1·1–3·6)	0·030	2·7 (1·4–5·2)	0·004	3·2 (1·9–5·4)	<0·0001
Physician diagnosed eczema by 2 years	3·8 (1·9–7·8)	0·0002	1·1 (0·4–3·3)	0·9	2·0 (1·0–4·1)	0·047
Early wheezing phenotype						
Transient early	1·6 (0·7–3·5)	0·3	2·0 (0·8–4·8)	0·14	1·4 (0·7–2·9)	0·3
Late onset	5·4 (2·5–11)	<0·0001	4·6 (1·7–12)	0·003	7·4 (3·9–14·0)	<0·0001
Persistent	8·9 (4·0–20)	<0·0001	4·0 (1·2–14)	0·027	14·0 (6·8–28)	<0·0001
Alternaria skin-test positive at 6 years	2·0 (1·0–4·0)	0·067	0·6 (0·2–2·2)	0·4	3·6 (2·1–6·4)	<0·0001
CA-BHR at 6 years	2·4 (0·9–6·5)	0·083	6·9 (2·3–21·0)	0·0006	4·5 (1·9–10·0)	0·0006
Lowest V′maxFRC quartile at 6 years	1·1 (0·5–2·4)	0·8	2·8 (1·1–6·9)	0·029	2·1 (1·1–3·9)	0·021

Multinomial odds ratio (M-OR) estimated with multinomial logistic regression with all risk factors listed in the table included in the model with the no asthma group as the reference group. Models were additionally adjusted for ethnicity, sex, and current smoking at age 22 years. CA-BHR=bronchial hyperresponsiveness to cold air challenge at age 6 years. V′maxFRC=lowest quartile compared to upper three quartiles combined.

Table 5: **Multinomial odds ratio for asthma groups at age 22 years by different risk factors in early life**

first diagnosis between inactive and chronic asthma (32% *vs* 45% diagnosed at 2–6 years, 41% *vs* 35% diagnosed at 8–11 years, and 27% *vs* 21% diagnosed 13–16 years, respectively, p=0·2). However, there was a significant effect of age at diagnosis on the FEV_1/FVC ratio at age 22 years (figure). For both chronic and inactive asthma, age at diagnosis was significantly and linearly related to the FEV_1/FVC ratio (p=0·009) after adjusting for asthma status and sex.

Univariate and multinomial analyses for the association between early life risk factors and asthma at age 22 years are shown in tables 4 and 5, respectively. Newly diagnosed asthma was twice as likely in women as in men. Parental asthma and both late onset and persistent wheezing during the first 6 years of life were associated with inactive, newly diagnosed, and chronic asthma (tables 4 and 5 and the webfigure). By contrast, eczema by age 2 years and *A alternata* sensitisation at age 6 years were associated with inactive and chronic asthma but not with newly diagnosed asthma. Low V′maxFRC at age 6 years was associated with newly diagnosed and chronic asthma but not inactive asthma at age 22 years. There was a strong positive association between cold-air bronchial hyper-responsiveness and both newly diagnosed asthma (M-OR 6·9, 95% CI 2·3–21·0) and chronic asthma (4·5, 1·9–10·0). The population attributable risks of cold-air bronchial hyper-responsiveness for newly diagnosed and chronic asthma were 33% and 26%, respectively. Inactive asthma at age 22 years was not associated with cold-air bronchial hyper-responsiveness at age 6 years.

See Online for webfigure

Discussion

In over 70% of people with current asthma and 63% of those with newly diagnosed asthma at age 22 years, episodes of wheezing had happened in the first 3 years of life or were reported by parents at age 6 years (table 4). Cold-air bronchial hyper-responsiveness (but not sensitisation to *Alternaria*) at age 6 years, late-onset and persistent wheezing by 6 years, and female sex, were independent predictors of incident physician-diagnosed asthma at 22 years. Moreover, cold-air bronchial hyper-responsiveness and sensitisation to *Alternaria* at age 6 years, together with persistent and late-onset wheezing by that age, were independent predictors of chronic asthma. Early sensitisation to other allergens prevalent in other locations might show similar strong associations with adult asthma as seen with *Alternaria* in our study area. Male sex was a significant predictor of asthma remission. Our findings support our previous proposition that most forms of asthma have their origins in early life,[12] but we now extend that proposition to asthma diagnosed in early adult life.

Few studies have prospectively assessed the early-life risk factors for prevalent, incident, and remitted asthma in early adult life.[3] In the most comprehensive study, Strachan and co-workers[13] assessed the 1958 British cohort and reported a yearly incidence of asthma of 11·1 per 1000 person-years) among people age 17–33 years, which is much the same as the incidence of 12·6 per 1000 person-years between 16 and 22 years in our study. In Sweden, Larsson and colleagues[14] reported an incidence of 11·1 per 1000 person-years at age 16–19 years. In neither of the previous two studies, however, was prospectively obtained information from the first years of life available.

Both chronic and newly diagnosed asthma at age 22 were much more common (4·5 and 6·9 times more likely, respectively) in those with cold-air bronchial hyper-responsiveness at age 6 years than in those without (table 4), and this association was independent of current asthma symptoms by that age. These results suggest that asymptomatic changes in the regulation of airway tone are already present in preschool years and strongly predict the likelihood of having asthma in early adult life. Although we had previously shown that cold-air bronchial hyper-responsiveness at age 6 years is associated with allergic sensitisation at that age,[8] the association between this risk factor and incident physician-diagnosed asthma

at 22 years was independent of sensitisation to *Alternaria*.[11] However, people with newly diagnosed asthma were more likely to be sensitised to aeroallergens at 22 years than those with no asthma. These results strongly suggest that, much like chronic asthma, newly diagnosed asthma at 22 years is associated with the clinical expression of cold-air bronchial hyper-responsiveness already present in early childhood. However, and contrary to chronic asthma, newly diagnosed asthma is associated with late-onset sensitisation and is unrelated to early sensitisation to local aeroallergens.

Persistent wheezing in early childhood was a strong predictor of both chronic and incident asthma at 22 years. We had previously shown that transient early wheezing was unrelated to the risk of asthma symptoms at age 8–16 years, whereas persistent and late-onset wheezing were consistently associated with these symptoms in that age group.[1] We interpret these findings as indicating that children classified with persistent or late-onset wheezing in early life are predisposed to chronic symptoms that will either last throughout childhood or reappear more intensely in early adult life, especially in women.

Women were twice as likely as men to have asthma diagnosed at age 16–22 years (table 4). Moreover, more than 70% of participants with newly diagnosed asthma at age 22 were women. Conversely, men were more likely than women to have inactive asthma at age 22 years (table 4), suggesting higher rates of asthma remission in men age 16–22 years. These findings confirm and extend those recorded in several other longitudinal studies in this age group, which have suggested a gradual change in the prevalence of asthma between male and female individuals between the pubertal years and early adult life.[15–18]

As expected, mean FEV_1/FVC ratio was significantly lower at age 22 years in participants with both newly diagnosed and chronic asthma than in those with inactive asthma and no asthma (table 3). However, a positive response to bronchodilators was present only in people with chronic asthma, suggesting irreversible deficits in lung function in newly diagnosed asthma. Of particular interest was the fact that, in both inactive and chronic asthma, FEV_1/FVC ratio at age 22 years was strongly and linearly correlated with age at diagnosis assessed prospectively (figure). These findings support the notion that changes in airway structure and function are more likely when initiation of the airway inflammatory processes associated with childhood asthma happens in preschool years. However, chronic airway hyper-responsiveness in school years, even in the absence of symptoms, is associated with deficits in the normal increases in lung function that accompany child growth,[19] which might predispose to asthma in early adult life.

Active smoking was a strong predictor of asthma, current wheezing, and current shortness of breath with wheeze in early adult life. These findings are in agreement with those of other studies in this age group[20] and support the contention that deleterious effects on lung health can be detected soon after starting to smoke.

Our study has limitations that need to be taken into account when interpreting our findings. As with most long-term cohort studies, by age 22 we had lost track of over a third of participants and those remaining were better educated, less likely to belong to ethnic minority groups, and less exposed to parental smoking than those who withdrew from the study (table 2). Furthermore, almost half the participants at age 22 years had moved out of Tucson and could not be tested for lung function or allergy. Because of concerns about the ethics of doing airway challenges in very young children, we did not test for cold-air bronchial hyper-responsiveness at 6 years in children with current wheezing or those requiring active asthma treatment at that age; our results might, therefore, underestimate the association between this risk factor and chronic and incident asthma in early adult life. Finally, we relied on physician diagnosis reported by parental questionnaire to assess the presence of asthma at all ages. This epidemiological approach has been widely used to assess asthma incidence and prevalence both in longitudinal studies[21] and in national asthma surveys.[22,23] Although subject to diagnostic drift and bias, physician-diagnosed asthma is a strong indicator of need for health care use in people with asthma-like symptoms and thus allows differentiation of those with mild or misinterpreted wheezing episodes from those with symptoms needing physician attention. Indeed, almost two-thirds of all children without a diagnosis of asthma during follow-up had at least one report of wheezing at age 2–16 years. Our study should thus be interpreted as assessing risk factors for asthma symptoms significant enough to induce a diagnosis of asthma by a physician. Others have proposed use of objective markers, such as concomitant increased responses to salbutamol or methacholine to assess the presence of asthma in symptomatic patients.[24] We have previously shown, however, that each of these objective markers identifies different asthma phenotypes,[25] and thus their isolated use is likely to introduce analytical biases towards different forms of asthma that coexist during childhood and adolescence.

Our study confirms and extends to the first years of life the findings of two cohorts from New Zealand[26] and Australia,[27] which showed strong correlations between asthma symptoms, lung function, and bronchial responsiveness assessed during the school years and chronic asthma up to the fifth decade of life. We conclude that asthma that apparently develops in early adult life affects mainly women and is commonly the clinical expression of latent changes of airway responses that are present in the preschool years. From the point of view of public health, primary prevention of this form of asthma will only be possible when the genetic and environmental factors that determine these changes have been identified and their effects blocked or reversed.

Contributors

FDM designed the current study; DAS analysed the data under the direction of FDM; all authors interpreted the data; FDM and DAS wrote the report with input from the other authors.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

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Poor airway function in early infancy and lung function by age 22 years: a non-selective longitudinal cohort study

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Summary

Background Together with smoking, the lung function attained in early adulthood is one of the strongest predictors of chronic obstructive pulmonary disease. We aimed to investigate whether lung function in early adulthood is, in turn, affected by airway function measured shortly after birth.

Methods Non-selected infants were enrolled at birth in the Tucson Children's Respiratory Study between 1980 and 1984. We measured maximal expiratory flows at functional residual capacity ($Vmax_{FRC}$) in 169 of these infants by the chest compression technique at a mean of 2·3 months (SD 1·9). We also obtained measurements of lung function for 123 of these participants at least once at ages 11, 16, and 22 years. Indices were forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), and forced expiratory flow between 25% and 75% of FVC ($FEF_{25–75}$), both before and after treatment with a bronchodilator (180 µg of albuterol).

Findings Participants who had infant $Vmax_{FRC}$ in the lowest quartile also had lower values for the FEV_1/FVC ratio (–5·2%, p<0·0001), $FEF_{25–75}$ (–663 mL/s, p<0·0001), and FEV_1 (–233 mL, p=0·001) up to age 22, after adjustment for height, weight, age, and sex, than those in the upper three quartiles combined. The magnitude and significance of this effect did not change after additional adjustment for wheeze, smoking, atopy, or parental asthma.

Interpretation Poor airway function shortly after birth should be recognised as a risk factor for airflow obstruction in young adults. Prevention of chronic obstructive pulmonary disease might need to start in fetal life.

Introduction

30 years ago, Burrows and coworkers made the seminal observation that adults with a history of paediatric respiratory illness had lower levels of lung function and were more likely to develop obstructive lung disease than those without such a history.[1] One plausible interpretation of this finding is that respiratory infections can damage the lung and predispose to obstructive lung disease. However, events before any respiratory illness could also possibly predispose individuals both to these early illnesses and to subsequent chronic impairment of lung function.[2] Our findings and those of others[3–6] supported this contention, by showing that children who presented with illnesses of the lower respiratory tract during their first years of life had lower maximal expiratory flows than others shortly after birth and before any such illnesses developed. These results suggest the hypothesis that chronic obstructive pulmonary disease has origins in fetal life, and specifically in the factors that determine intrauterine growth of lungs and airways.

Longitudinal studies have suggested that a substantial proportion of deficits in lung function that present during the third decade of life, and especially those in individuals who have a diagnosis of asthma, persist into late adulthood and predispose for the development of chronic obstructive pulmonary disease.[7] We aimed to assess to what degree these deficits in lung function are already present in the early postneonatal period.

Methods

Participants

We enrolled 1246 healthy infants at birth, between 1980 and 1984, in the Tucson Children's Respiratory Study, a longitudinal non-selected cohort study.[8] We developed a chest-compression technique, for assessment of pulmonary function in infancy, as the last 376 infants were enrolled in the study. Of these 376 eligible infants, 20 could not be contacted within the testing time, 111 did not have the consent of their parents, 27 had a lower respiratory infection, 35 did not fall asleep, seven were older than 6 months, six changed health-care providers, and we did not have length information for one. We tested the remaining 169 infants shortly after birth, at a mean of 2·3 (SD 1·9) months. Details of the selection and exclusion criteria have been reported previously.[3] We obtained informed consent from participants or their parents each time lung function was measured. The study was approved by the institutional review board of the University of Arizona.

Procedures

We obtained partial expiratory flow-volume curves by the chest-compression technique and recorded the maximal expiratory flow at functional residual capacity ($Vmax_{FRC}$) for 169 infants.[4,9] We did follow-up spirometry for 123 of these individuals at three ages: 109 at a mean of 10·9 (SD 0·4) years, 87 at a mean of 16·8 (0·5) years, and 83 at a mean of 21·7 (0·6) years. At age 11 years, follow-up spirometry was done with a custom-built, pneumotachometer-based system, running software on a portable

computer,[10] and at ages 16 and 22 with a portable Schiller Spirovit SP-1 (Schiller AG, Baar, Switzerland).[11] We calibrated these systems with a Jones flow-volume calibrator (Model FVC-3000; Jones Medical Instrumentation Company, Oakbrook, IL, USA). No children had used a bronchodilator within 6 h of testing. After we took baseline measurements, a fixed dose of two puffs of albuterol (180 µg) was administered from a metered-dose inhaler and aerochamber-holding device (Monaghan Medical Corp, Plattsburgh, NY, USA), and we did postbronchodilator spirometry after 15 min. Spirometry indices included the forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), and forced expiratory flow between 25% and 75% of the FVC ($FEF_{25–75}$). We calculated the response to bronchodilation for all spirometric indices as at ages 11, 16, and 22, as follows:

$$\frac{\text{postbronchodilation measurement}-\text{prebronchodilation measurement}}{(\text{postbronchodilation measurement}+\text{prebronchodilation measurement})} \times 100$$

We did methacholine challenge tests at age 11, and defined bronchial hyper-responsiveness as values for methacholine-dose response below the tenth percentile for a healthy reference subgroup (who had negative skin tests, and neither had wheeze, nor had been diagnosed with asthma), as previously reported.[12] Study nurses recorded height, weight, and age at the time of testing.

At enrolment, parents completed a questionnaire about their ethnicity, history of physician-diagnosed asthma, years of education, age, and smoking. We also gathered information about pregnancy and delivery for each participating infant. We noted any lower respiratory illnesses that had been confirmed by a physician from birth to 3 years of age, and any concurrent symptoms recorded by the physician.[13] Any occurrence of wheeze during the previous year was determined by a questionnaire completed at every follow-up (11, 16, and 22 years). We did skin-prick tests with six local airborne allergens (Hollister-Stier Laboratories, Everett, WA, USA) at ages 11, 16, and 22 years, as previously described.[14] Tests were read after 20 min, and wheal size was recorded as the sum of the two diameters at right angles to each other; wheal sizes of greater than 3 mm were recorded as positive. Participants who had at least one positive skin-prick test were classed as atopic. Active smoking was assessed from salivary cotinine concentrations (>10 ng/mL) at age 16 years (competitive radioimmunoassay; Foundation for Blood Research, Scarborough, ME, USA) and by self-completed questionnaire at age 22 years.

Statistical Analysis

Airway function measured in infancy ($Vmax_{FRC}$) was logarithmically transformed (base e), adjusted for infant length, and standardised to the average length of the infants at 2 months of age (57·4 cm) as previously reported.[4] We used length-adjusted infant $Vmax_{FRC}$ either as a continuous variable (natural logarithm of mL/sec) or as a categorical predictive variable (grouped into quartiles). Follow-up spirometry indices at ages 11, 16, and 22 years (FVC, FEV_1, $FEF_{25–75}$, and the FEV_1/FVC ratio) were normally distributed. For separate analyses at each survey, the follow-up spirometry indices were adjusted for concurrent height, weight, and sex, and the standardised residuals used as the outcome measure. We used Pearson correlation to assess the relation between normally distributed continuous variables. R^2, calculated as the square of the Pearson correlation coefficient, was used to estimate the proportion of variability explained by infant airway function.

We assessed follow-up spirometry longitudinally by use of a random-effects model,[15,16] with age, height, and weight as time-dependent covariates, and gender and infant $Vmax_{FRC}$ as time-independent covariates (webpanel). We also assessed other covariates that were associated with participants (ethnicity, early lower respiratory illnesses, wheeze, active smoking, and atopy) and with their parents (history of physician-diagnosed asthma, years of education, age, and smoking history). Potential confounders and covariates were entered separately in the basic random-effects model. Covariates related to any of the follow-up spirometry indices with

See Online for webpanel

	TCRS infant-testing group	All TCRS participants	p*
Participant characteristics			
Sex (male)	65/123 (53%)	548/1123 (49%)	0·4
Ethnicity (non-Hispanic white)	76/123 (62%)	658/1123 (59%)	0·5
LRI before age of 3 years	54/102 (53%)	465/786 (59%)	0·2
RSV LRI before age of 3 years	45/102 (23%)	184/764 (24%)	0·7
Atopic at age 6 years†	45/115 (40%)	245/646 (38%)	0·8
Active wheeze at age:			
11 years	26/122 (21%)	228/827 (28%)	0·2
16 years	23/107 (22%)	168/632 (27%)	0·3
22 years	47/101 (47%)	235/623 (38%)	0·09
Maternal characteristics			
Asthma	13/122 (11%)	114/1033 (11%)	0·9
Smoking	24/123 (20%)	196/1120 (18%)	0·6
Education (>12 years)	95/123 (77%)	752/1118 (67%)	0·02
Age (>28 years)	51/123 (42%)	428/1122 (38%)	0·5
Paternal characteristics			
Asthma	22/114 (19%)	110/980 (11%)	0·01
Smoking	34/121 (28%)	351/1105 (32%)	0·4
Education >12 years	89/121 (74%)	767/1096 (70%)	0·4
Age >28 years	71/121 (59%)	589/1109 (53%)	0·2

TCRS=Tucson Children's Respiratory Study. LRI=lower respiratory infections. RSV=respiratory synctial virus. Data are number (%) unless indicated otherwise. *p values based on Pearson χ^2 statistic. †At least one positive reaction in a skin-prick test.

Table 1: **Baseline characteristics of participants in our study compared with all others enrolled in the Children's Respiratory Study**

See Online for webtable 1

See Online for webtable 2

See Online for webfigure

	11 years* (n=109)		16 years* (n=87)		22 years* (n=83)	
	r	p	r	p	r	p
Prebronchodilator test						
FEV_1/FVC ratio	0·38	<0·0001	0·32	0·003	0·34	0·002
FEF_{25-75}	0·34	0·0003	0·33	0·002	0·30	0·006
FEV_1	0·18	0·06	0·18	0·09	0·18	0·1
FVC	−0·03	0·7	−0·03	0·8	−0·07	0·5
Postbronchodilator test						
FEV_1/FVC ratio	0·26	0·007	0·28	0·01	0·30	0·006
FEF_{25-75}	0·31	0·001	0·28	0·01	0·27	0·01
FEV_1	0·09	0·4	0·14	0·2	0·13	0·2
FVC	−0·06	0·6	-0·02	0·9	−0·04	0·7

r=Pearson correlation coefficient. *Spirometry indices of lung function were regressed with height, weight, and sex; standardised residuals were saved and used as outcome measures. $Vmax_{FRC}$ measured in infancy was logarithmically transformed, adjusted for length, and standardised to the average length of the infants at 2 months of age.

Table 2: **Correlation between $Vmax_{FRC}$ of infants and lung function at ages 11, 16, and 22**

p<0·1 and covariates with biological significance, were retained for analysis with a final multifactorial model. Two-sided p values of less than 0·05 were regarded as significant. We analysed data with STATA (version 9.0) and SPSS (version 14.0) statistical software.

See Online for webtable 3

Results

The 123 participants included in our study had more educated mothers (p=0·02) and more fathers with asthma (p=0·01) than the other 1123 children enrolled in the Children's Respiratory Study (table 1). Other than that, the baseline characteristics of the two groups did not differ.

Length-adjusted infant $Vmax_{FRC}$ did not seem to be associated with potential confounders such as birthweight or type of delivery, or parental ethnicity, asthma, smoking, age, or level of education (webtable 1). These results did not change when the analyses were stratified by sex (data not shown). However, male participants had lower infant $Vmax_{FRC}$ than did female participants (p=0·003).

Unadjusted baseline spirometry indices for male and female participants at ages 11, 16, and 22 years are shown in webtable 2. $Vmax_{FRC}$ in infants, adjusted for body length, was correlated with FEV_1/FVC ratio and FEF_{25-75}, adjusted for height, weight, and sex, at ages 11, 16, and 22 years (table 2 and webfigure). Infant airway function accounted for between 9% and 14% of the variability in subsequent adjusted FEV_1/FVC ratio and FEF_{25-75} at ages 11, 16, and 22 years. No association was noted between length-adjusted infant VmaxFRC and adjusted FVC and FEV_1 at any separate survey (p=0·05). Infant $Vmax_{FRC}$ was less closely correlated with postbronchodilator FEV_1/FVC ratio and FEF_{25-75} than with prebronchodilator measures of airway function, but correlation coefficients remained significant at ages 11, 16, and 22 years (table 2). Length-adjusted $Vmax_{FRC}$ was associated with subsequent FEV_1/FVC ratio and FEF_{25-75} in both male and female participants at ages 11, 16, and 22 years, although with small fluctuations in statistical significance at different ages (webtable 3).

A longitudinal random-effects model was used to assess the relation between length-adjusted infant $Vmax_{FRC}$ and subsequent lung function. Infant $Vmax_{FRC}$ was directly associated with subsequent prebronchodilator FEV_1/FVC ratio (p<0·0001) and FEF_{25-75} (p<0·0001) up to the age of 22 years, after adjustment for age, height, weight, and sex (table 3). In the longitudinal model, infant $Vmax_{FRC}$ was directly associated with FEV_1

	FEV_1/FVC ratio		FEF_{25-75} (mL/s)		FEV_1 (mL)		FVC (mL)	
	β (SE)	p	β (SE)	p	β (SE)	p	β (SE)	p
Prebronchodilator								
Infant $Vmax_{FRC}$ (ln of mL/s)	4·7% (1·0)	<0·0001	566 (128)	<0·0001	168 (64)	0·009	−2·8 (72)	0·9
Age (years)	−0·4% (0·1)	<0·0001	−8·5 (12·7)	0·5	18·2 (6·8)	0·007	41·0 (8·0)	<0·0001
Height (cm)	0·1% (0·03)	0·007	51·6 (4·4)	<0·0001	45·7 (2·4)	<0·0001	49·5 (2·8	<0·0001
Weight (kg)	−0%6 (0·02)	0·009	−2·4 (3·0)	0·4	2·5 (1·6)	0·1	6·8 (1·8)	0·0002
Sex (male)	−1·9% (1·0)	0·052	140 (129)	0·3	305 (65)	<0·0001	464 (72·7)	<0·0001
Model Constant	56% (6)	<0·0001	−7617 (787)	<0·0001	−5653 (407)	<0·0001	−5480 (464)	<0·0001
Postbronchodilator								
Infant $Vmax_{FRC}$ (ln of mL/s)	3·1% (0·8)	<0·0001	489 (124)	<0·0001	113 (60)	0·061	−2·4 (68)	0·9
Age (years)	−0·2% (0·1)	0·031	17·0 (14·8)	0·2	26·6 (7·0)	<0·0001	40·6 (8·0)	<0·0001
Height (cm)	0·06% (0·03)	0·048	49·8 (5·1)	<0·0001	44·7 (2·4)	<0·0001	48·5 (2·8)	<0·0001
Weight (kg)	−0·06% (0·02)	0·003	−1·5 (3·2)	0·6	2·5 (1·6)	0·10	6·6 (1·8)	0·0002
Sex (male)	−2·1% (0·8)	0·010	42·6 (126)	0·7	312 (61·0)	<0·0001	460 (68·9)	<0·0001
Model Constant	68% (5)	<0·0001	−6943 (821)	<0·0001	−5274 (394)	<0·0001	−5305 (447)	<0·0001

Random-effects models of data for 123 individuals with 279 total follow-up spirometry data points, before and after bronchodilation. Age, height, and weight were entered as time-dependent covariates; infant $Vmax_{FRC}$ and sex as time-independent covariates.

Table 3: **Association between infant $Vmax_{FRC}$ and lung function at ages 11, 16, and 22 years**

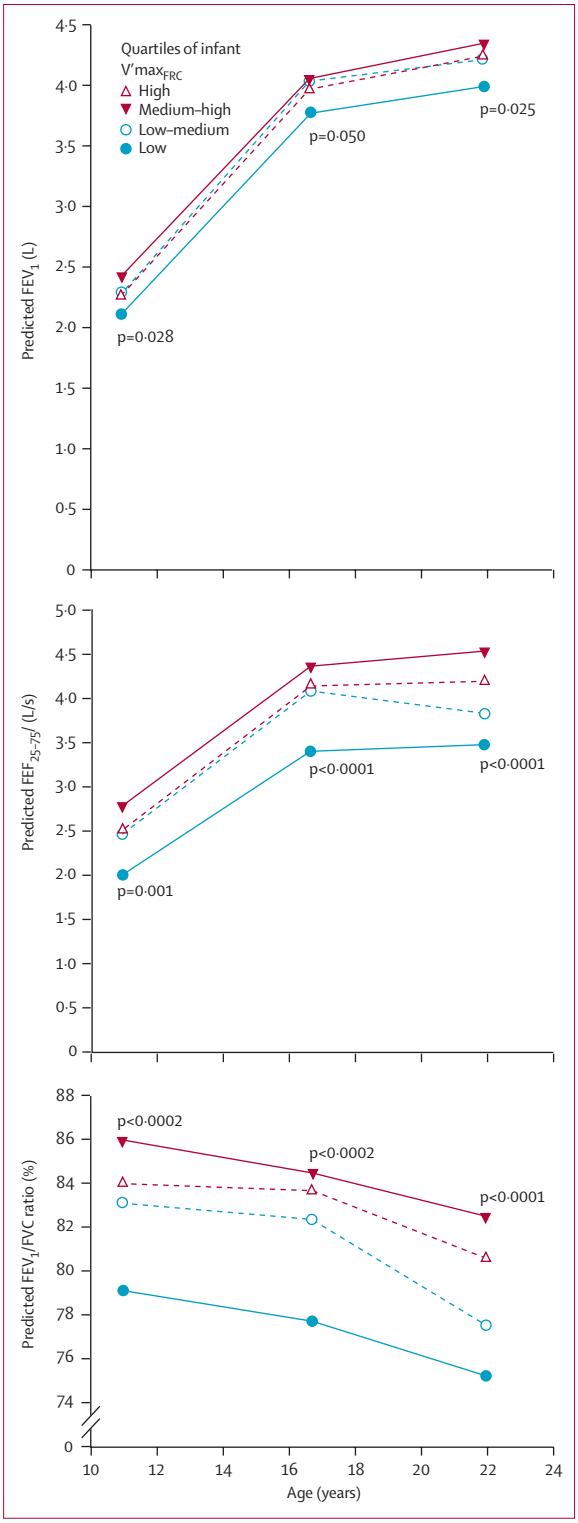

Figure: **Predicted mean values for lung function in males at ages 11, 16, and 22 years by length-adjusted infant Vmax$_{FRC}$**

Predicted values were standardised to the mean height and weight for male participants at ages 11, 16, and 22 years. We included an interaction term between survey (age 11, 16, and 22) and quartiles of infant Vmax$_{FRC}$ in the random-effects models. P values were estimated at each survey from the models.

(p=0·009), but there was no association with FVC. Only wheeze and atopy, tested in the models as time-dependent covariates, and active smoking by the participant at ages 16 or 22 years or both, met the cutoff for inclusion in the random-effects models (p<0·1); maternal smoking at enrolment was also retained. When the models shown in table 3 were repeated to include wheeze, atopy, and smoking, the magnitude and significance of the relation between infant Vmax$_{FRC}$ and subsequent lung function did not change (webtable 4). The associations between infant lung function and postbronchodilator FEV$_1$/FVC ratio and FEF$_{25–75}$ were similar to those calculated by use of prebronchodilator values, although the association between infant lung function and postbronchodilator FEV$_1$ did not reach statistical significance (table 3 and webtable 5).

See Online for webtable 4

See Online for webtable 5

The relation between infant Vmax$_{FRC}$ and subsequent lung function was assessed separately in male and female participants by stratifying the longitudinal models by gender. Length-adjusted Vmax$_{FRC}$ was directly associated with subsequent prebronchodilator FEV$_1$/FVC ratio and FEF$_{25–75}$ in both male and female participants (webtable 3), but not with FEV$_1$ or FVC after adjustment for height, weight, and age. The associations between infant lung function and postbronchodilator FEV$_1$/FVC ratio and FEF$_{25–75}$ did not differ widely by sex of participant (webtable 3).

The relation between infant Vmax$_{FRC}$ and subsequent lung function was further assessed by grouping infant Vmax$_{FRC}$ into quartiles. The figure shows the use of random-effects models to plot the predicted values for FEV$_1$, FEV$_1$/FVC ratio and FEF$_{25–75}$ for male participants by quartiles of length-adjusted infant Vmax$_{FRC}$. Participants in the lowest quartile for infant Vmax$_{FRC}$ had persistently diminished values for FEV$_1$/FVC ratio (–5·2% [95% CI: –7·4 to –3·0], p<0·0001), FEF$_{25–75}$ (–666 mL/s [–955 to –378], p<0·0001) and FEV$_1$ (–234 mL [–377 to –91], p=0·001) up to age 22 years compared with the upper three quartiles combined (after adjustment for height, weight, age, and sex). Moreover, age did not interact with infant Vmax$_{FRC}$. Similar results were obtained for the lowest quartile for infant Vmax$_{FRC}$ and adjusted post-bronchodilator FEV$_1$/FVC ratio (–3·6% [–5·4 to –1·9], p<0·0001), FEF$_{25–75}$ (–602 mL/s [–881 to–322], p<0·0001) and FEV$_1$ (–176 mL [–311,–42], p=0·1) through age 22 years compared with the upper three quartiles.

Infant Vmax$_{FRC}$ was inversely related to bronchodilator response for FEV$_1$/FVC ratio at 11 and 22 years, and FEV$_1$ at 22 years (webtable 6). When assessed with the random-effects model, infants with Vmax$_{FRC}$ in the lowest quartile had greater responses to bronchodilation for FEV$_1$/FVC ratio (1·18% [95% CI 0·4, 1·9], p=0·002), FEF$_{25–75}$ (3·37% [0·9, 5·8], p=0·006) and FEV$_1$ (1·38% [0·4, 2·4], p=0·006) through age 22 years compared with the upper three quartiles combined. By contrast, the proportion of 11-year-old children with bronchial hyper-responsiveness

See Online for webtable 6

	Sex (male)	Ethnicity (non-Hispanic white)	Lower respiratory illness	Atopic at 6 years	Maternal		Wheeze		
					Asthma	Smoking	11 years	16 years	22 years
Infant $Vmax_{FRC}$									
First quartile (23·1–78·3 mL/s)	18/27 (66·7%)	16/27 (59·3%)	20/26 (76·9%)	11/27 (40·7%)	4/26 (15·4%)	5/27 (18·5%)	7/27 (25·9%)	5/23 (21·7%)	12/23 (52·2%)
Second quartile (79·0–119·1 mL/s)	22/33 (66·7%)	19/33 (57·6%)	13/25 (52·0%)	14/30 (46·7%)	4/33 (12·1%)	10/33 (30·3%)	7/33 (21·2%)	7/33 (26·9%)	12/26 (46·2%)
Third quartile (120·3–165·7 mL/s)	14/31 (45·2%)	20/31 (64·5%)	11/25 (44·0%)	7/29 (24·1%)	1/31 (3·2%)	6/31 (19·4%)	6/30 (20·0%)	4/28 (14·3%)	9/24 (37·5%)
Fourth quartile (167·3–242·3 mL/s)	11/32 (34·4%)	21/32 (65·6%)	10/26 (38·5%)	13/29 (44·8%)	4/32 (12·5%)	3/32 (9·4%)	6/32 (18·8%)	7/30 (23·3%)	14/28 (50·0%)
Trend χ^2	0·003	0·5	0·005	0·8	0·5	0·2	0·5	0·8	0·8
Infant $Vmax_{FRC}$									
Lower quartile (23·1–78·3)	18/27 (66·7%)	16/27 (59·3%)	20/26 (76·9%	11/27 (40·7%)	4/26 (15·4%)	5/27 (18·5%)	7/27 (25·9%)	5/23 (21·7%)	12/23 (52·2%)
Upper three quartiles (79·0–242·3)	47/96 (49·0%)	60/96 (62·5%)	34/76 (44·7%)	34/88 (38·6%)	9/96 (9·4%)	19/96(19·8%)	19/95 (20·0%)	18/84 (21·4%)	35/78 (44·9%)
Pearson χ^2	0·1	0·8	0·005	0·8	0·4	0·9	0·5	0·9	0·5

Data are number (%), unless stated otherwise.

Table 4: **Infant lung function as $Vmax_{FRC}$ and characteristics of infants**

to methacholine was unrelated to their $Vmax_{FRC}$ as infants (28·6%, 27·8%, 25·0%, and 31·3% for the lowest to highest quartiles respectively, trend χ^2 p=0·9).

Table 4 shows that, concordant with previous reports from this same cohort,[3] infants in the lowest quartile for $Vmax_{FRC}$ had an increased risk for development of lower respiratory illnesses in the first 3 years of life (77%) compared with children in the upper three quartiles combined (45%, p=0·005). Infants in the lowest quartile did not differ in ethnicity, sex, or maternal asthma or smoking from those in the upper three quartiles, and they were not more likely to have wheeze at ages 11, 16, or 22 years (table 4).

Discussion

We showed that up to 14% of the variance in measurements of airway function (FEV_1, FEV_1/FVC ratio, and $FEF_{25–75}$) in young adults was related to the maximal flows at functional residual capacity ($Vmax_{FRC}$), measured in the same individuals at 2 months. Infant lung function was correlated with all measurements of airway function at ages 11–22 years, but more strongly with measurements taken before bronchodilator use than with those after bronchodilation. Moreover, individuals who had low airway function as infants had much greater responses to bronchodilators than others. We did not measure infant lung function after bronchodilator use, and thus we do not know if the weaker association between infant lung function and bronchodilator responsiveness was due to variability between individuals in congenital responses to bronchodilators. However, both reversible and irreversible determinants of maximal flows during forced expirations could explain the correlations recorded before bronchodilator administration. We recorded no association between infant lung function and subsequent bronchial responses to methacholine, which suggests that structural characteristics of the lung, and not intrinsic airway hyper-responsivess, were responsible for the recorded tracking of airway function from birth to early adult life (ie, individuals remained at a constant deviation from the mean over time).

A detailed analysis of our data suggested that the correlation between infant airway function and lung function in adult life could be attributed to some individuals in whom airway function was already diminished shortly after birth. These individuals, who were so classified because they were in the lowest quartile for length-adjusted infant $Vmax_{FRC}$, had, for example, mean predicted FEV_1/FVC ratios of 75·1% (95% CI 73–77) at age 22 years, which was 5·2% lower than mean values for infants in the other three quartiles. This finding suggests that individuals with airflow obstruction at birth will be more likely to remain in the lowest end of the distribution until early adult life, whereas tracking of airway function might be less evident in children with normal airways. However, we cannot exclude the possibility that, by use of the passive chest-compression technique to obtain partial flow-volume curves,[9] maximal flows could have been more readily obtained in infants with congenitally narrower airways than in those with larger airway. If this were the case, however, our results would underestimate the correlation between infant airway function and lung function obtained with full flow-volume curves in older children and adults.

Previous studies had shown that spirometric parameters tracked within cohorts during school age.[17,18] Our results suggest that the lowest levels of airway function can be tracked from shortly after birth, and that individuals who are born with low $Vmax_{FRC}$ have persistently poor lung function up to 22 years of age. Similarly, Turner and colleagues[19] reported that airway function in infancy was positively correlated with lung function measured at ages 6 and 11 years in children with different wheezing phenotypes. Filippone and co-workers[20] reported that in children with bronchopulmonary dysplasia, airway function tracks from age 2 to 9 years. Hoo and colleagues[21]

showed strong tracking of airway function between birth and 9 months of age in infants of both normal and low birthweight. Taken together, these findings support the hypothesis that factors which control airway development in utero determine the degree of airway function that an individual will attain by early adult life. This hypothesis is compatible with the observation that branching of the bronchial tree is complete by 16 weeks of gestation,[22] and that the number of terminal bronchiolar duct endings does not increase postnatally.[23] Elastic recoil also affects maximal expiratory flow,[24,25] not only because it is the motive force behind flow, but also because it maintains airway patency, or openness. We did not measure static recoil because methods of measurement are invasive. It is, however, not inconceivable that our findings could be explained by life-long changes in the static recoil of the lung, either alone or in combination with altered airway conductance.

The main strength of our study was the large proportion of participants in our newborn cohort for whom airway function was measured shortly after birth and one or more times thereafter up to the age of 22 years. Nevertheless, we did not test a sufficient number of infants to allow us to accurately determine the relative contributions to lung function in early adult life of congenital deficits in airway function and of acquired factors such as lower respiratory infections, ongoing symptoms, and environmental exposures.

With data obtained from these participants, we previously showed that children who wheezed during viral infection in the first years of life, and especially those whose symptoms had remitted before the age of 6 years (so-called transient wheezers), had lower premorbid $Vmax_{FRC}$ than children who never wheezed during the preschool years.[4] Other long-term birth-cohort studies had previously shown that adults who had lower respiratory illnesses in early life had worse lung function than those with no such history.[26] Our results suggest that in-utero alterations in airway development predispose individuals both to lower respiratory illnesses and to subsequent deficits in lung function during adult life. This hypothesis does not exclude the possibility that lower respiratory illnesses in early life, especially in children whose symptoms persist beyond the preschool years, might themselves cause additional deficits in development of lung function that become apparent after birth.[11] Moreover, other studies have shown that passive smoking,[27] air pollution,[28] and other factors,[29] can affect airway function.

Chronic obstructive pulmonary disease is the fourth leading cause of death in the USA,[30] and is projected to become the third leading cause of death worldwide by 2020.[31] Its defining characteristic is irreversible airflow obstruction, which is conventionally defined as a postbronchodilator FEV_1/FVC ratio of 70% or lower.[32] Although cigarette smoking is known to be the major risk factor for this disease,[33–35] 5–10% of non-smoking young adults and up to 30% of non-smoking adults aged 65 years or older have evidence of chronic obstructive pulmonary disease.[36] In non-smokers, impaired lung function is also a known predictor of mortality due to ischaemic heart disease and stroke.[37] Individuals who enter adult life with lung-function deficits are at risk of chronic obstructive pulmonary disease in their later adult years, especially if they had lower respiratory illnesses in early life.[38] In our cohort, infants who had lung function in the lowest quartile started adulthood with deficits in FEF_{25-75}, FEV_1, and the FEV_1/FVC ratio. We postulate that, even if the lung function of these individuals was to diminish during adult life at rates similar to those recorded in non-smokers,[39] they would reach the threshold of FEV_1 and FEV_1/FVC ratio that define chronic obstructive pulmonary disease[32] at an earlier age than their peers. Fetal determinants of airway function could therefore predispose not only to airflow obstruction and chronic obstructive pulmonary disease, but also to non-respiratory morbidity and mortality during adult life.

The factors that affect pulmonary development in utero are not well understood. Lung morphogenesis is a highly regulated process that could be impaired in utero by both genetic and environmental factors.[40] Among these factors, maternal smoking during pregnancy has been consistently associated with poor lung function in both infants[41,42] and older children.[43] Children with chronic lung disease of prematurity have impaired lung function growth,[44] as do, to a lesser extent, premature children who did not have chronic lung disease of prematurity.[45] Our results suggest that a better understanding of the mechanisms that control normal lung growth in utero would contribute to development of strategies for the prevention of chronic obstructive pulmonary disease in adult life.

Contributors

FDM designed the study, and DAS analysed the data with input from FDM. WJM did the infant pulmonary function tests. All authors contributed to interpretation of the data. FDM and DAS drafted the manuscript with input from WJM, SG, and ALW. All authors approved the final version of the manuscript.

Conflict of interest statement

We declare that we have no conflict of interest.

Role of the funding source

The funding source had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Current reviews of allergy and clinical immunology
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Tucson Children's Respiratory Study: 1980 to present

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This activity is available for CME credit. See page 41A for important information.

The Tucson Children's Respiratory Study (TCRS), begun in 1980, has followed 1246 subjects from birth together with their family members to delineate the complex interrelationships between a large number of potential risk factors, acute lower respiratory tract illnesses, and chronic lung disorders later in childhood and early adult life, especially asthma. Nine hundred seventy-four (78%) of the original subjects are still being followed. Among its numerous findings, the TCRS has (1) described various wheezing disorders (transient, nonatopic, atopic) and their characteristics; (2) developed an Asthma Predictive Index; (3) delineated the respiratory and atopic outcomes for children who had respiratory syncytial virus–related wheezing illnesses in infancy; and (4) evaluated a large number of risk factors for acute respiratory tract illnesses during the first 3 years of life. Future TCRS studies will focus on (1) factors in infancy and early childhood that relate to persistent asthma and atopy; (2) role of genetic factors in persistent asthma; and (3) determinants of lung function decline in early adult life. (J Allergy Clin Immunol 2003;111:661-75.)

Key words: *Asthma, risk factors, wheezing syndromes, atopy, lower respiratory tract illnesses, Tucson Children's Respiratory Study, lung function, immunology*

The Tucson Children's Respiratory Study (TCRS) was begun in 1980 as a long-term, longitudinal study to investigate the interrelationships between a large number of potential risk factors, acute lower respiratory tract illnesses (LRIs) during the first 3 years of life, and the development of chronic lung disorders, especially asthma, in later childhood and young adult life.[1] By enrolling a large number (N = 1246) of infants at or soon after birth, this cohort study was designed to minimize or avoid many of the problems of previous studies. The strengths of the study include the following: (1) extensive pre-LRI data, including lung function and assessment of various immunologic and allergic parameters; (2) enrollment of a large number of subjects and their family members; (3) a predominantly outpatient population, thereby avoiding the biases of a hospitalized population; (4) extensive data relating to a large number of risk factors (infectious, physiologic, genetic, familial, psychosocial, immunologic, allergic, and environmental) (Table I); (5) extensive microbiologic, virologic, and serologic data relating to the acute LRIs; and (6) long follow-up period with excellent retention of enrolled subjects/families.

The design of the TCRS has facilitated the assessment of the natural history and sequelae of acute LRIs and their relationship, either independent of or in concert with certain other risk factors, to the development of chronic lung disorders, especially asthma, later in life.

Enrollment of index subjects and their families occurred during a 4½-year period, 1980 to 1984. Data have been collected from all family members at numerous time points (Tables II through IV) to maximize pre-illness and follow-up information and to minimize issues related to recall bias. Certain key demographic data are summarized in Table V. The study was originally designed to enroll 1000 neonates and their families. This was predicated on a 25% cumulative rate for LRIs during the first 3 years of life and a 20% to 25% cumulative loss rate during the first 5 years of the study. In fact, the LRI rate was nearly 46% and the dropout rate was 13% during the first 5 years. The overall loss rate has averaged 1.3% per year. LRIs were only studied during the first 3 years of life. Enrollment was extended beyond 1000 to apply newly described tests of lung function for infants[2,3] to a relatively large group of very young babies. This last group of enrollees also afforded the opportunity to do certain tests of immune function early in life, before any LRIs. At present, 974 or 78% of the initial group remain in the study, with 60% still in Tucson. This large number of remaining subjects bodes well for future follow-up studies. The extensive amount of pre-LRI, pre–chronic lung disease, acute LRI, and risk factor data have facilitated many analyses summarized in subsequent sections.

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TABLE I. Potential risk factors evaluated for possible relationships with acute LRI or chronic lung disease (asthma)

Sex, ethnicity
Birth weight
Parents' education, income, age
Respiratory symptoms and illnesses in other household members
Genetic determinants
Number and order of siblings
Bottle/breast-feeding
Day care
Type of home heating, cooking, and cooling
Number and type of pets
Indoor air pollution
Passive/active smoking
Atopy
Immune function
Lung function
Airway reactivity

TABLE II. Data collection

Enrollment (birth)
Questionnaire (family) data
Maternal pregnancy history
Cord blood (IgE, immune studies)
CBC/differential
Periodic data
Well-baby visit forms
Periodic questionnaires on all household members
2 to 3 months of age
Pulmonary function tests
9 to 15 months of age
IgE, CBC and differential, immune studies
LRIs in first 3 years of life
Sign/symptom and history forms
Cultures, serologies, CBC and differential, IgE
Convalescence (3-5 wk post LRI) serologies, IgE, CBC and differential

CBC, Complete blood count.

TABLE III. Number of index subjects in the CRS with data at each evaluation

	Early years of life	In-depth I	In-depth II	In-depth III
Age of index subjects	Birth to 3 y	6 y	11 y	16 y
Respiratory questionnaires*	1055 (age 2 y)	1025	955	509†
LRI evaluations through age 3 y	888	—	—	—
Skin prick tests	—	762	689	397†
Serum IgE	1120 (at birth)	550	633	357†
Peripheral blood eosinophils	880 (at 9 mo)	550	633	357†
Pulmonary function studies	176 (at 4 mo)	676	595	376†
Airway challenge studies	—	368	396	303†
Peak flow variability	—	—	600	383†

*Respiratory questionnaires were also obtained on the enrolled child at age 3 (n = 940), 8 (n = 841), and 13 (n = 714) years. Questionnaires are also being obtained at age 18, but this is still in progress.
†Data collection is still in progress.

Abbreviations used

CRT: Childhood respiratory trouble
FRC: Functional residual capacity
LRI: Lower respiratory tract illness
OR: Odds ratio
RSV: Respiratory syncytial virus
TCRS: Tucson Children's Respiratory Study
$V'_{max}FRC$: Maximal forced expiratory flow at functional residual capacity
WLRI: Wheezing lower respiratory illness

The successes of the TCRS during the past 22 years are attributable to many factors; some of the most important are the following:

1. The use of 1 large HMO, which helped the study avoid economic extremes of the population and facilitated follow-up. Minimal fees for well-baby and acute LRI follow-up visits were great advantages.
2. Involvement by 1 large group of pediatricians who were very interested in the study and participated actively, especially with enrollment and evaluation of LRIs. The pediatricians did the initial approach to the new parents (usually while the mothers and neonates were still in the hospital) regarding enrollment in the study. Enrollment of the index subjects predominantly occurred immediately after delivery; some were enrolled at the 2-week well-child visit. The very high enrollment rate of 78% (Table V) was directly attributable to the pediatricians' extensive involvement.
3. Available space in the HMO offices for the study nurses. Most of the evaluations during the first 5 years of the study were done in the offices of the pediatricians.
4. Long-term involvement by the study nurses (1 nurse has been with the TCRS for 20 years). This allowed the nurses to become very well-acquainted with the enrolled families.
5. Extensive participation, retention, and follow-up methodologies.
6. Lower than anticipated loss rate and higher than expected LRI rate.
7. Minimizing blood draws; being able to do 1 blood draw in the neonatal period at the time of the phenylketonuria test for IgE levels, certain immune tests, and cotinine levels while obtaining a screening hematocrit for the pediatricians. Similarly, at 9

to 15 months of age, the pediatricians routinely checked a hematocrit, which allowed the study nurses to obtain blood for IgE, certain immune tests, and cotinine and to store sera. Except during acute LRIs, infants only had blood drawn for study tests when blood was being drawn for routine clinical assessment.

8. Being able to obtain cord bloods (through the cooperation of the obstetricians in the HMO) for certain analyses.
9. Development of tests of lung function applicable to young infants.
10. Having an outstanding virology laboratory that produced a 62% isolation rate.

This review will summarize the major findings from the TCRS since its inception in 1980 and planned future studies.

ACUTE LRIs

Acute LRIs are common early in life, with rates being highest in infancy. Parents of children in the TCRS were requested to take their children to the pediatrician whenever the child developed certain symptoms (deep or "wet" cough, wheeze, stridor, etc). The pediatrician recorded all relevant signs and symptoms, and nasopharyngeal/throat swabs were obtained for viral culture. The prevalence of wheezing with LRIs in the TCRS among children followed for the entire year was 32.0%, 17.3%, and 12.0% in the first, second, and third years of life, respectively. An etiologic agent was identified, by culture or direct immunofluorescence for antigen detection, in 66% of LRIs.[4] Children for whom an etiologic agent was identified did not differ from those who were culture-negative in clinical characteristics or seroconversion to other respiratory viruses.[5] As anticipated from previous studies,[6,7] respiratory syncytial virus (RSV) was the most common agent identified, followed by parainfluenza virus type 3. Multiple etiologic agents were observed for approximately 24% of episodes.[8]

Several behavioral or environmental factors were associated with risk of having LRIs. Breast-feeding of at least 1 month was associated with lower rates of wheezing LRIs during the first 4 months of life.[9] Further, there appeared to be an interaction between infant feeding practices and other risk factors for RSV infection (such as sharing the room, low maternal education, and low maternal RSV titer), such that the protective effect of breast-feeding was particularly evident for those with additional risks.[9,10] Children of younger mothers were significantly more likely to develop wheezing LRIs compared to children whose mothers were 30 years old or older.[11] Wheezing LRIs were also more common among children who had evaporative coolers in their homes.[12] Use of day care in the presence of 3 or more children was associated with roughly double the risk for LRI[13] from the age of 4 months to 3 years. Maternal smoking was associated with a significantly higher incidence of wheezing LRI in infancy[14,15] and with earlier age of first LRI. In the third year of life, the risk of a wheezing LRI in the presence of a smoking caregiver was 3 times higher than for children who did not have a smoking caregiver.[13] There were no significant gender differences in LRIs early in life.

One unanticipated finding was the observation that nonwheezing LRIs appeared to influence IgE production. Children were divided into 3 groups depending on their LRI history during the first 3 years of life: those who had wheezing LRIs, those with nonwheezing LRIs only, and those with no LRIs.[16] Children who had only nonwheezing LRIs in early life did not differ from never wheezers in terms of IgE production at birth. However, they produced significantly less IgE at 9 months and 6 years. Further, children whose nonwheezing LRIs occurred after blood was drawn at 9 months had normal IgE levels at 9 months but had significantly decreased IgE at 6 years (relative to never wheezers). Because the children with nonwheezing LRIs also had higher IFN-γ levels at 9 months, it is possible that their ability to mount a T-cell response had matured earlier than those who had wheezing LRIs. Alternatively, IgE production in middle childhood may be altered by nonwheezing LRIs, at least in certain hosts.

TABLE IV. Evaluation of family members at in-depth I

	Mothers	Fathers	Siblings
Questionnaire	1008	908	1150
Pulmonary function tests	840	671	625
Blood sample	806	635	540
Allergy skin tests	813	664	847
Methacholine studies	319	272	51

TABLE V. Summary of certain demographic data

Category	Number (%)
Families approached for enrollment	1760
Total eligible for enrollment	1596
Enrolled infants and families	1246 (78)
Number of cord blood specimens	1084 (87)
CBC and differential at time of phenylketonuria test	947 (76)
IgE, CBC and differential at 9-15 mo	959 (77)
Number of children with LRIs, first 3 y	572 (46)
Number of acute LRIs, first 3 y	1052
Number with culture specimens during LRIs (percent is of those referred for acute studies)	756 (88)
Number with pulmonary function tests at 2-3 mo of age	192

ENVIRONMENTAL, SOCIOECONOMIC, AND GENDER STUDIES

One of the most important findings from the TCRS is that events occurring early in life appear to be important determinants of subsequent asthma. For example, umbilical cord blood IgE shows no relation to later asthma. However, IgE near the end of the first year of life is associated with later persistent wheezing and asthma,[15] which suggests that some event in the first year of life

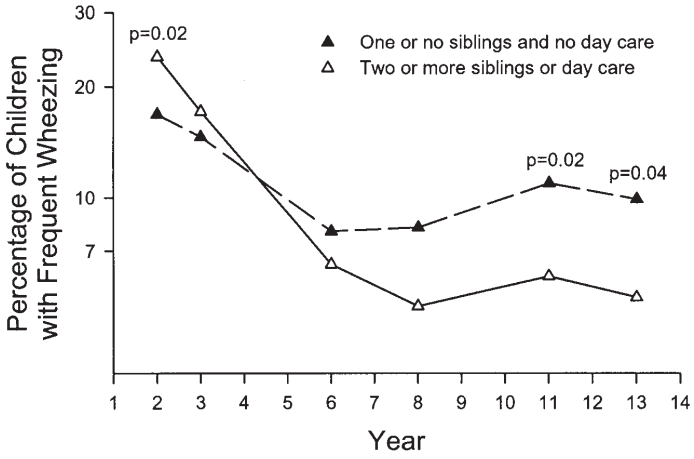

FIG 1. Frequent wheeze by sibling/day care groups in first 6 months of life (from Ball TM, Holberg CJ, Martinez FD, Wright AL. Exposure to siblings and day care during infancy and subsequent development of asthma and frequent wheeze. N Engl J Med 2000;343:538-43).

either alters or unmasks a child's propensity to respond in an allergic fashion.

It has been hypothesized that the reduction in microbial burden that has occurred during the past century in the industrialized world may have altered normal postnatal immune system development,[17] particularly the regulation of the allergen-specific immune responses that underlie allergy. Three findings from the CRS are consistent with this hypothesis. First, we assessed[18] the relation between exposure to other children during the first 6 months of life to wheezing both early in life and later. After adjustment for potential confounders, each additional older sibling in the home (odds ratio [OR], 0.80; 95% CI, 0.66 to 0.96) and attendance in day care during the first 6 months of life (OR, 0.55; 95% CI, 0.32 to 0.94) were found to protect against the development of current physician-diagnosed asthma between ages of 6 to 13 years. In addition, infants exposed to more children at home or day care experienced more frequent wheeze at year 2 (OR, 1.56; 95% CI, 1.14 to 2.12) but less frequent wheeze from year 8 (OR, 0.53; 95% CI, 0.37 to 0.76) through year 13 (OR, 0.25; 95% CI, 0.14 to 0.45). Skin test reactivity at both age 6 and 11 years and elevated serum IgE levels were also inversely related to increased exposure to children at home or in day care during early infancy. Thus, although exposure to children at home or in day care during infancy increased wheeze in early life, it appears to be protective against the development of atopy, asthma, and frequent wheeze in school age children (Fig 1).

A second analysis[19] considered the relation between exposure to pets in early life and the time to first report of frequent (more than 3 episodes in the past year) wheezing. We found that children living in households with 1 or more indoor dogs at birth were less likely to develop frequent wheeze than those not having indoor dogs ($P = .004$). This inverse association was confined to children without parental asthma (hazard ratio, 0.47; $P < .001$, Cox regression) and was not evident for children with parental asthma (hazard ratio, 0.96; $P = .87$). Adjustment by potential confounders did not change the results. Indoor cat exposure was not significantly associated with the risk of frequent wheezing. Neither cat nor dog exposure in early life was associated with skin prick test reactivity or total serum IgE level at any age.

Finally, infant feeding practices may play a role in the development of allergy and asthma. First, the relation of maternal IgE level to IgE level in the child appears to be altered by infant feeding practices. Breast-feeding was associated with lower total serum IgE level at age 6 years for children whose mothers were in the lower 2 terciles of the distribution of IgE. In contrast, breast-feeding was associated with higher IgE level at age 6 years for children whose mothers had high IgE level.[20] We also found that children with maternal asthma were significantly more likely to have asthma if they had been exclusively breast-fed (OR, 8.7; 95% CI, 3.4 to 22.2).[21] This relationship was only evident for atopic children and persisted after adjusting for confounders. Breast-feeding is protective against a wide range of infections, which obviously provided a critical selective advantage under the conditions in which the immune system of *Homo sapiens* evolved. However, these benefits of breast-feeding may reduce the stimulus for maturation of antimicrobial immunity in the context of reduced exposure to microbes, particularly among infants who are doubly susceptible by virtue of both a parental history of asthma and their own atopy.

In the TCRS, although the point prevalence of wheeze declined, the prevalence of active asthma diagnosed by a physician increased at each survey until age 16 years, the last age at which data are currently available. In addition, distinct gender differences were evident (Fig 2). Boys were significantly more likely to wheeze early in life, especially at age 6 and 8 years, and the prevalence of wheeze declined steadily with increasing age. For girls, however, the prevalence of wheeze declined in the first decade of life but then began to increase. Consequently, gender differences in wheeze became borderline at age 13 years ($P < .08$) and disappeared completely by age 16 years ($P < .96$). Similarly, although physician-diagnosed

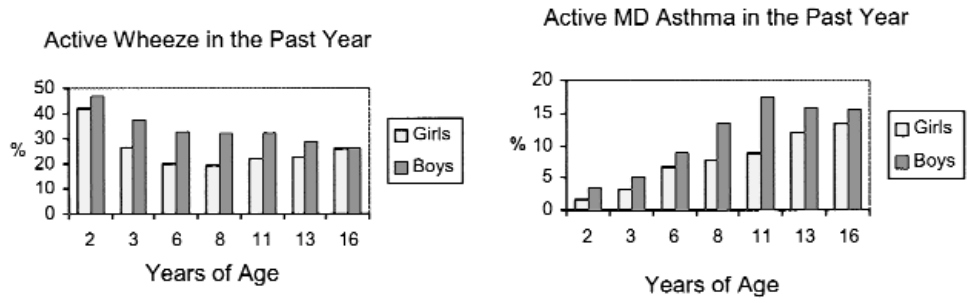

FIG 2. Percent of TCRS children with wheeze *(left)* and active physician-diagnosed asthma *(right)* in the past year, by age and gender.

asthma was more common in boys at all ages, it increased during the first decade of life but then declined for boys starting at age 11 years. For girls, however, active asthma continued to increase through age 16 years (Fig 2). Of particular interest in this context is the finding that girls, but not boys, who were overweight or obese at age 11 years were more likely to have current wheezing at ages 11 and 13 years but not at ages 6 or 8 years.[22] This effect was strongest among girls who started puberty before the age of 11 years. Girls who became overweight or obese between 6 and 11 years were up to 7.1 times more likely to develop new asthma symptoms at age 11 or 13 years than those who did not ($P = .0002$), and they were also significantly more likely to have increased bronchodilator responsiveness and increased variability of peak flow at the age of 11 years. This finding suggests that increase in weight during the preschool years is associated with an increased risk of developing new asthma symptoms and increased bronchial responsiveness in early adolescence for girls.

GENETIC STUDIES

The TCRS was initially conceived as a longitudinal study of the risk factors for and potential sequelae of respiratory diseases. At that time, in 1979, genetic epidemiology per se, and of asthma specifically, was essentially in its infancy. The implementation of the TCRS in 1980 occurred at a most opportune time to take advantage of the growth and development of genetic studies. Thus, although not initially designed as a genetic study per se, the study population (families comprising the index child, all siblings, and both parents, enrolled at random with respect to respiratory diseases) is ideally suited to many forms of genetic analyses. In addition, as genetic studies mature, it is becoming clear that there are important interactions occurring between genes and the environment, which may arise only within a particular time window. Longitudinal studies are essential to defining phenotypes based on, for example, early life events; the longitudinal TCRS data set is particularly relevant and invaluable in this regard. The study of the genetics of asthma in the TCRS has included a broad spectrum of analytic methods, keeping pace with new genetic technologies.

The earliest TCRS genetic studies used classic epidemiologic methods to examine parental histories of childhood respiratory trouble (CRT) as risk factors for LRIs in their infants.[23] After controlling for confounders, a parental history of CRT described as asthma or bronchiolitis with onset before age 3 years was associated with wheezing LRIs in their children (OR, 2.6; $P < .05$), whereas parental CRT described as bronchitis/croup was associated with nonwheezing LRIs in their offspring. Such classic epidemiologic approaches give an indication of familial aggregation within the data but do not indicate whether the trait may be inherited genetically following Mendelian principles. The statistical detection of Mendelian ratios in the transmission of a trait from one generation to another, known as segregation analysis, was the next approach.

Asthma has been characterized as a complex phenotype; the disease is heterogeneous with variability in age of onset and presentation, including the possibility of remission; environmental factors play a crucial role in its expression, and a number of pathogenic processes appear important in its clinical expression. This variation suggests that the disease is not under the control of a monogenic 2-allele locus, but that several major and minor loci plus a strong environmental determinant may be involved in its expression. Given the characterization of asthma as a complex phenotype, there has been considerable emphasis on studying the genetics of phenotypes showing a strong association with asthma, which may also cluster within families. The supposition is that such "intermediate phenotypes," or more specifically the genes regulating their expression, may play a crucial role in the pathogenesis of asthma.[24] Segregation analysis was applied to a number of asthma phenotypes, drawing the study populations from 1151 nuclear families enrolled in the TCRS. The first analysis for total serum IgE levels indicated that the best fit to the data was a model of Mendelian codominant inheritance of a major autosomal gene associated with higher serum IgE level.[25] Tests for genetic heterogeneity showed no significant difference between the 2 ethnic groups (Hispanic and non-Hispanic white). The initial success in statistically identifying a Mendelian major autosomal gene for IgE was not matched in subsequent segregation analyses with other phenotypes, including a self-report of physician-

diagnosed asthma, FEV_1, and the level of circulating eosinophils. For each of these phenotypes, although there were significant parent-offspring and sibling-sibling correlations, results indicated the rejection of the hypothesis of a single 2-allele locus. For the diagnosis of asthma phenotype, either a polygenic/multifactorial mode of inheritance alone or an oligogenic mode, with some evidence of a recessive component, were compatible with the data.[26] Results suggested that lung function is inherited in a polygenic/multifactorial fashion, with evidence of a Mendelian recessive component associated with higher levels of lung function and a genetic or maternal influence in asthmatic families.[27] For eosinophil levels, the results suggested an oligogenic mode of inheritance with an infrequent recessive Mendelian component for low eosinophil levels in non-Hispanic white families.[28] Collectively, these results support the concept of multiple, relatively common genes, interacting to determine genetic susceptibility to asthma.

Concurrent with the statistical modeling approaches, linkage analyses using the sibling pair approach with polymorphic microsatellite markers and association studies assessing known and novel polymorphisms identified by sequencing techniques were begun. The focus of these studies has been mainly on a candidate region in chromosome 5q 31-33, where the interleukin cluster of genes is found.

The earliest TCRS association study reported that subjects with a different genotype for a polymorphism reported by Liggett[29] in the β_2-adrenoreceptor (at amino acid 16 in the coding region [Arg-16]) on chromosome 5q31-33 show differences in the prevalence of positive responses to bronchodilators.[30] Subsequently, linkage of circulating eosinophils, as a percent of total white blood cells, to markers located on chromosome 5q31-33 was demonstrated in this area, and a multipoint analysis showed that the maximal logarithm of the odds favoring genetic linkage (LOD score) was observed for marker D5S658.[31] Further linkage studies showed that a compound atopy-related phenotype obtained by factor analysis demonstrates significant evidence for linkage with markers in 5q31-33, but an "asthma" phenotype, after atopy had been controlled for, showed no evidence for linkage with these same markers.[32] These results suggest that variants in gene(s) in chromosome 5q may determine atopy and, through this mechanism, increase susceptibility to asthma. However, there appear to be no variants that determine asthma independent of the atopic status. A search for variants in this area, which may be associated with these linkage signals, led to the discovery of a number of novel polymorphisms. In the TCRS population, a polymorphism in the 5′ flanking region of the CD14 gene is associated with circulating soluble CD14 levels and with total serum IgE level.[33] The CD14 gene maps to chromosome 5q31.1. Also reported are 7 polymorphisms (6 novel) in IL-13[34]; 4 of these are tightly linked to a variant in the terminal portion of the coding region of the gene that results in a predicted amino acid change in residue130 (Arg130Gln). The Gln form is strongly associated (P = .000002) with increased serum IgE levels in 3 different populations (TCRS and 2 German populations) comprising a total of 1399 children.

IMMUNOLOGIC AND ATOPIC STUDIES

The prospective, longitudinal design of the TCRS, the breadth of phenotypic data, and the more recent addition of genetic information provide opportunity to relate the maturation and regulation of the immune system to acute LRIs in early life and to the development of asthma, allergy, and asthma-related and allergy-related traits and risk factors. The immunology arm of the TCRS was originally designed to test the premise that IgE responses were critical to and likely causative in the development of allergy and asthma. Longitudinal epidemiologic data can provide evidence for genetic regulation in a phenotype if significant tracking occurs within individuals. Data on the index children of the TCRS obtained at birth, at age 9 months, and at 5-year intervals thereafter showed significant tracking of serum IgE levels from birth onward.[35] These data established that regulatory mechanisms for serum IgE levels were already in place at birth despite the very low cord blood values that increase more than 30-fold by 9 months and 300-fold by 11 years of age. IgE levels (once values are above the threshold of detection) provide a log normally distributed variable in the population in keeping with its origin from B cells that class switch as they proliferate in response to antigen stimuli.

Two allergy-related events have shown significant relations to cord blood IgE. The first is the direct predictive relation to the development of eczema in the first year of life.[36] Second is the changing relationship of cord IgE to the prevalence of acute viral LRIs, inverse in the first year of life[36] and direct in the third year.[37] This changing relationship led to further analyses showing that both the children beginning to have LRIs in the third year and those starting with LRIs in the first few years of life and continuing to have them were the children most susceptible to chronic wheezing and asthma.

Cord blood IgE levels did not show an association with the development of asthma; thus the regulatory mechanisms described above appear to be independent of the development of asthma. However, subsequent studies[38] showed that IgE levels were increased acutely during the first LRI in those children who went on to wheeze persistently compared to those who wheezed transiently and only with LRIs in the first year or two of life (Fig 3, *A*).[38] These data support the possibility that children destined to develop persistent wheezing are already "programmed" immunologically before the first LRI to respond differently to a respiratory viral infection. Further support for the hypothesis is provided by this same study that showed that blood eosinopenia, long known to occur with many viral illnesses, did not occur in those children who went on to become persistent wheezers (Fig 3, *B*).[38] IgE levels obtained at ages subsequent to birth do show a relation to asthma; thus IgE levels appear to be regulated both by mechanisms evident at birth that are independent of asthma and by mechanisms regulating responses to environ-

mental insults that enhance or reveal susceptibility to asthma. Whether IgE levels in the latter situation contribute to or simply occur in parallel to asthma development remains an important issue for further study.

The TCRS also provided the opportunity to define the major offending allergens (as detected by skin test responses) in relation to persistent wheezing or asthma at age 6 years.[39] The only allergen skin test responses significantly associated with physician-diagnosed asthma were those to *Alternaria alternata*. Bermuda grass was a much more frequent sensitizer in the general population but did not show a significant association to asthma, and other common local aeroallergens did not also. Interestingly, and despite its frequent association with asthma worldwide, *Dermatophagoides farinae* was an infrequent sensitizer and was not significantly associated with asthma in the TCRS enrollees raised in the Tucson semiarid environment.

As described in the previous genetics section, the TCRS has also provided a rich source of genetic-based immune regulation data that have altered the original premise of a causative role for IgE in asthma development because the data showed that, despite the marked association of total serum IgE with asthma prevalence, the 2 had distinct inheritance patterns. Total serum IgE levels provided evidence for a major gene inherited via a codominant Mendelian mechanism.[25] The familial pattern of asthma inheritance, in contrast, was typical of a complex disease (without evidence for a major gene), and removing total IgE from the analysis did not affect the results.[26] Also, the prevalence of asthma in children, although significantly influenced by parental asthma, was found to be unrelated to parental IgE level (Fig 4; unpublished observations).

As an alternate to the concept that IgE is a major causative factor of asthma, the hypothesis has been put forth that asthmatic airway inflammation may be brought about by T_H2 cells with activities that are independent of their role in initiating IgE synthesis. To test this possibility, we sought evidence for a link between asthma and T_H2 cytokine production from peripheral blood T cells. These studies showed a direct relation between the capacity to produce IL-4 and IgE level[40] and an indirect relation between the capacity to produce IFN-γ early in life and subsequent immediate skin test reactivity.[41] However, they did not show an association between asthma and T_H2 biased cytokine production[40] (manuscript in preparation). Thus, the TCRS studies have altered the concept of IgE acting in a causative role in the development of asthma and alternatively suggest that the close association of IgE levels and asthma might occur by the concept in reverse, ie, as a result of asthma regulating IgE levels by mechanisms different from the IgE regulating mechanisms in the nonasthmatic population.

Further analyses provided evidence for 2 subphenotypes of asthma, one diagnosed most commonly before age 3 years, showing risk related to early life LRIs, high rate of remission between ages 6 and 11 years, no relation to skin tests, but still related to total IgE. A second form of asthma defined by those with positive *Alternaria* skin

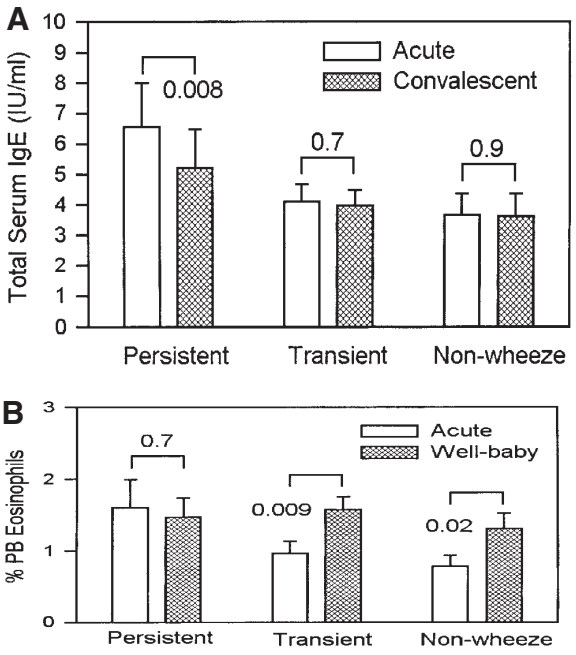

FIG 3. Differences in total serum IgE **(A)** and peripheral blood *(PB)* eosinophil levels **(B)** during and after the first LRI for children grouped as to their subsequent age 6 wheezing patterns. Group sizes for paired bars from *left* to *right* are 49, 88, and 42 for **(A)** and 33, 66, and 43 for **(B)**. Note that children who go on to wheeze chronically do show an acute increase in serum IgE with LRI and do not show the eosinopenia typical of the LRIs in the other children. (From: Martinez FD, Stern DA, Wright AL, Taussig LM, Halonen M. Differential immune responses to acute lower respiratory illness in early life and subsequent development of persistent wheezing and asthma. J Allergy Clin Immunol 1998;102:915-20.)

tests was diagnosed most commonly during or after age 3 years, was unrelated to early life LRIs, did not remit significantly by age 11 years, and was directly associated with total IgE.[42] Whether these forms of asthma occur in distinct subpopulations with different bases of susceptibility seems likely but remains to be determined.

The factors that cause asthma remain unidentified. Evidence is accumulating that both environmental and genetic factors can interact through the innate immune system to provide inhibition of asthma in those individuals who might otherwise be susceptible. Large and variable environmental exposures may influence the immune system (which is in turn genetically variable among individuals) in ways that result in varying degrees of resistance to the development of asthma and allergic manifestations. Recent studies have shown the importance of single nucleotide polymorphisms in the promoter region of the gene for the lipopolysaccharide receptor, CD14, in regulating the level of soluble CD14 and IgE level.[43] Although in our studies a relationship of CD14 genotype to the prevalence of asthma or allergy was not evident, this may have been due to sample size because others have reported a relationship to allergic symptoms.[44] It is unlikely that single nucleotide polymorphisms in a single gene will account for the complex disease phenotype of asthma. Additional studies of this

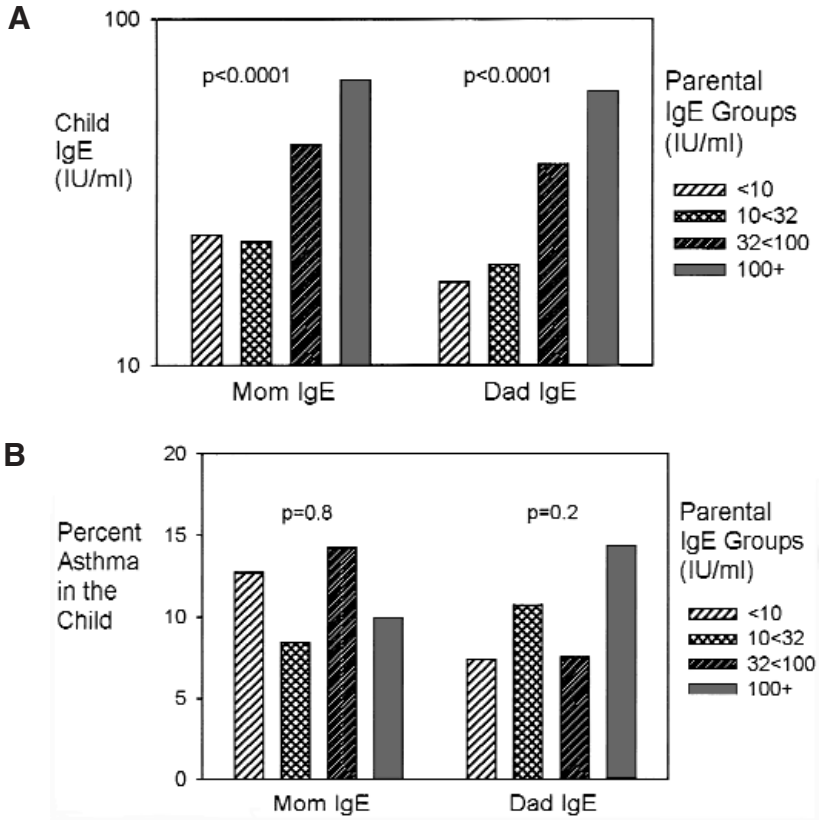

FIG 4. Relationship of child's serum IgE **(A)** and the child's prevalence of asthma **(B)** at age 6 to parental IgE levels. Parental IgE levels are grouped in half log intervals. Ordinate for **(A)** is logarithmic with values given as antilogs. Group sizes in **(A)** from low to high IgE groups for mom are 124, 111, 132, 133, and for dad are 55, 75, 108, 146; group sizes for mom in **(B)** are 181, 178, 190, 172 and for dad are 81, 103, 159, and 196. Note that parental IgE levels significantly influence the IgE level in the children but not the prevalence of asthma.

type are ongoing to identify the role of genetic diversity in the gene for CD14 and in genes for other factors that influence immune responses in ways that may significantly impact the balance between susceptibility and resistance to allergic disease.

PHYSIOLOGIC STUDIES

The prospective measurement of lung function has enabled the TCRS to characterize the impact of wheezing illness on lung development from infancy through adolescence. These measurements have also been central to the evolution of the hypothesis that asthma is a developmental disease determined by the interaction of the immune and respiratory systems in early life. Before the design of the TCRS, several epidemiologic studies had demonstrated a strong association between childhood respiratory troubles and diminished lung function in adulthood.[45] Because these studies were retrospective in nature, however, they suffered from several limitations including substantive recall bias.[46] Also, they could not determine whether early childhood respiratory illness led to decreases in lung function or the converse, ie, that diminished airway conductance led to an increased risk for wheezing in response to viral infections. The TCRS was designed to answer this question by recruiting subjects at birth; thus the relationship between respiratory illness and lung function development has been explored in a truly prospective manner.

Infant lung function was measured by using safe, noninvasive methods including rapid thoracic compression for the measurement of forced expiratory flow, helium dilution measurement of functional residual capacity (FRC), forced oscillation measurement of respiratory conductance, and tidal breathing analysis.[3,47] The rapid thoracic compression method allows the measurement of maximal forced expiratory flow at functional residual capacity ($V'_{max}FRC$) from partial expiratory flow-volume curves. Early in the development of this methodology, additional non-TCRS subjects were recruited to characterize the growth and development of the lung in healthy infants from 8.5 to 25 months after conception.[47,48] This study demonstrated that the highest size-corrected flows ($V'_{max}FRC/FRC$) were seen in newborns and healthy premature infants with values of 2.5 to 2.7 FRC/s. However, with the rapid postnatal growth of lung volume, size-corrected flows decreased by 50% to 1.2 FRC/s, a value that is comparable to older children and adults and that remained relatively constant from 13 to 25 months after conception. Finally, female infants had higher absolute and size-corrected flows than did male infants.

These findings suggested a physiologic basis to the clinical observation that most infantile wheezing lower respiratory illnesses (WLRIs) occur after the neonatal period and that male infants appear to have more severe, if not more prevalent, WLRI. They also suggest that the increased prevalence of WLRI early in life cannot be explained simply by a global reduction of airway conductance in all infants relative to older children and adults.

These infant lung function methodologies were developed relatively late in the TCRS recruitment period; thus only a subset of the 1246 TCRS infants were eligible for lung function testing. Analysis of 124 TCRS infants who had lung function measured before any LRI has led to a greater understanding of risk factors for WLRI in the first 3 years of life.[3] Infants who went on to have at least one WLRI in the first year of life demonstrated diminished respiratory system conductance and alterations in tidal expiration compatible with smaller airways before any LRI. Analysis of WLRI outcomes during the first 3 years of life further supported the relationship between premorbid decreases in lung function and increased risk for WLRI. Those infants who wheezed at least once during the first year of life and had at least 1 additional lower respiratory tract illness by 3 years of age demonstrated 22% lower initial levels of respiratory system conductance and 25% lower initial levels of $V'_{max}FRC$. On the basis of these studies, we concluded that diminished airway function both precedes and predicts recurrent wheezing in the first 3 years of life. This suggests that at least some of the reduction in maximal forced expiratory flow seen in adults who had childhood respiratory troubles may be due to premorbid differences in lung function as opposed to WLRI-associated damage to the developing airway.

Another potential explanation for the high prevalence of WLRI in infancy may be a relative increase in airway reactivity as compared to older children and adults. Airway response to cold, dry air challenge was assessed in 30 healthy infants compared to 12 control subjects who had $V'_{max}FRC$ measured in a similar manner but without any challenge.[49] Although the control group showed no significant change in $V'_{max}FRC$, the cold, dry air group had a mean reduction in $V'_{max}FRC$ of 18%, ie, about 1 intrasubject standard deviation. Combined with data from Tepper,[50] this suggests that even healthy infants have relatively reactive airways. Further, Young et al[51] have shown that in some infants this reactivity may be related to a family history of asthma and parental smoking. Thus, the long-held view that infants do not demonstrate airway reactivity and only wheeze as a result of mechanical obstruction by mucosal edema or luminal secretions has been effectively disproven by these studies of infantile airway response. Indeed, work by Shen et al[52] in rabbits has suggested that airway responsiveness to a nonspecific challenge decreases with age. Such a decrease in airway reactivity with age may explain the decrease in the frequency of wheezing illnesses with age in children who had RSV infections in infancy.[53]

Follow-up of 826 TCRS subjects with data from the first 3 years of life and at age 6 years has demonstrated, however, that diminished growth in airway function can occur in association with recurrent wheezing respiratory tract illness.[15] At the age of 6 years, 51.5% of all children had never wheezed (never wheeze), 19.9% had had at least 1 WLRI during the first 3 years of life but had no wheezing at 6 years (transient wheeze), 15% of all children had no wheezing in the first 3 years but had wheezing at 6 years of age (late wheeze), and 13.7% had wheezing both before 3 years of age and at 6 years (persistent wheeze). Thus, of those subjects who had wheezing before age 3 years, 59% had stopped wheezing by age 6 years. Not surprisingly, this early transient wheeze group had diminished lung function both in infancy and at 6 years of age when compared to children who never wheezed. The persistent wheeze group had $V'_{max}FRC$ values in infancy that were no different from those of the children who never wheezed. By age 6 years, however, the persistent wheeze group had the lowest lung function of the 4 groups with a significant reduction in $V'_{max}FRC$. Lung function in the late wheeze group was no different from that of the never wheeze group at both ages. Fig 5 shows $V'_{max}FRC$ at infancy and 6 years of age expressed as the mean Z-score for each of the 4 groups. The persistent wheezing group demonstrated a decline in lung function from infancy to 6 years, perhaps as a result of recurrent or ongoing airway damage during this period of rapid lung growth. Compared to children who never wheezed, the persistent wheeze group also had higher IgE levels at 1 and 6 years of age and were more likely to have mothers with a history of asthma and to have a physician's diagnosis of asthma. This suggests that the growth of airway function in the persistent group may have been modified by chronic airway inflammation. Although the observed deficits in $V'_{max}FRC$ could have been due to recurrent viral illness in the first 3 years, this seems unlikely because it was not seen in the transient wheeze group, who actually tended to improve their lung function (Fig 5). An important question at this time is whether this deficit in lung function and risk for asthma in high risk children could be prevented by regular anti-inflammatory therapy during the preschool years.

Airway reactivity at age 6 years was assessed using a cold, dry air challenge.[54] Hyperresponsiveness to cold air at age 6 years was associated with the subsequent development of asthma from age 6 to 11 years; however, this was not significant after adjusting for atopy and mild wheezing at age 6. This suggests that the hyperresponsiveness was a biomarker for the development of asthmatic airways due to ongoing allergic inflammation but not an independent risk factor for asthma. Subjects returned for spirometry and methacholine challenge testing at 11 years of age; they also performed 2 weeks of twice daily home peak flow measurement. Neither methacholine hyperresponsiveness nor increased peak flow variability was associated with wheezing that occurred only in the first 3 years of life. However, both measures of airway reactivity were increased in children who wheezed at both 6 and 11 years of age. Peak flow variability was associated with wheezing up to 6 years of age but not at

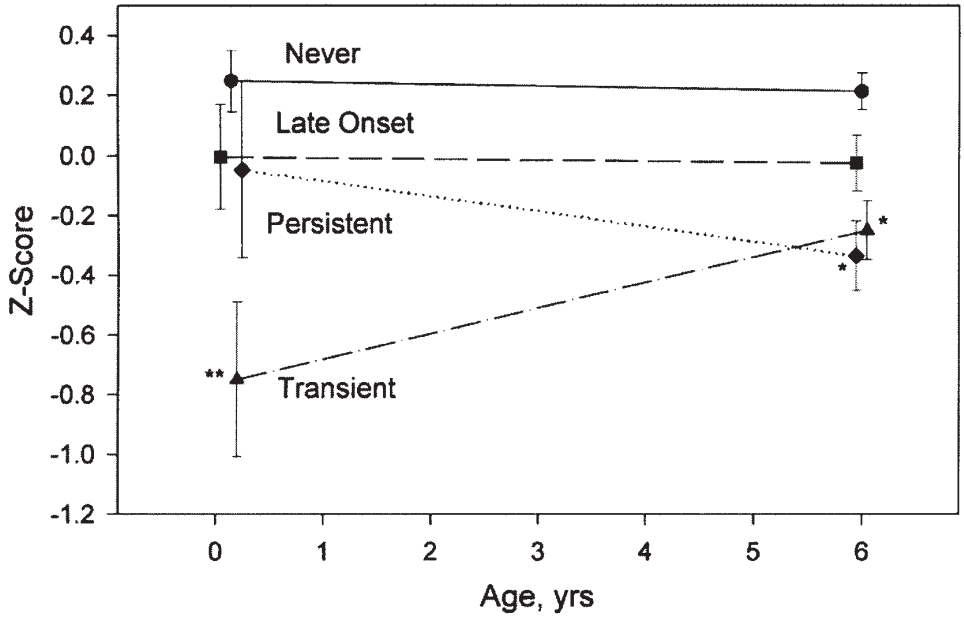

FIG 5. Lung function ($V'_{max}FRC$) at infancy and 6 years of age expressed in Z-scores by wheezing group: ●, never wheeze; ▲, transient early wheeze; ■, late onset wheeze; ◆, persistent wheeze. (*$P < .05$ vs never wheeze group; **$P < .05$ vs never, late, and persistent wheeze groups.)

age 11 in nonatopic children. Methacholine hyperresponsiveness was seen more frequently in boys and was strongly associated with serum IgE levels at age 6 and 11 years. In contrast, peak flow variability was not related to either gender or serum IgE.[55] These findings have helped to confirm and further refine the 3 wheezing phenotypes seen in childhood, which will be discussed later.

Physiologic studies in the TCRS have also clarified the relationship between specific patterns of LRI in early life and later outcomes. The incidence of radiologically confirmed pneumonia in the TCRS population was 7.4% in the first 3 years of life,[56] and the most common etiology defined was RSV (36.4%). Children who had pneumonia were more likely to have a physician diagnosis of asthma by age 11 years and to have lower levels of $V'_{max}FRC$ in infancy and at age 6 years. Children who had RSV-associated LRI in infancy also demonstrated decreased FEV_1 and forced expiratory flow at 25% to 75% of forced vital capacity at age 11 years, which were partly reversible by bronchodilator administration. This suggests that pneumonia in early life is perhaps at one end of the spectrum of viral respiratory illness and that children at risk for later asthma are more likely to develop radiographic changes of air space disease that could represent true pneumonia or simply atelectasis. Although premorbid deficits in lung function could be demonstrated in children who went on to get pneumonia, the number of subjects in this group who had lung function measured in infancy was small, and more work needs to be done to elucidate whether the reductions in lung function seen later in life are predominantly premorbid or due to longer-term chronic airway inflammation in at-risk children.

CHRONIC COUGH, CROUP, OTITIS MEDIA, AND COLIC

Cough variant asthma, first described in 1972,[57] is considered to be a mild form of asthma frequently unrecognized, resulting in inadequate treatment.[58] Risk factors for recurrent cough in childhood and its relation to asthma were assessed in the TCRS. Findings suggested that recurrent cough in the absence of wheeze differs in important respects from asthma.[59] Children having recurrent cough without wheeze were not different from those without symptom for serum IgE levels, skin test response, size corrected forced expiratory flow, or percent decline in flows after cold air challenge. Conversely, those with recurrent cough and wheeze had significantly more respiratory illness, more atopy, lower flow at end-tidal expiration, and greater decline in lung function after cold air challenge than those with neither symptom. In addition, in multivariate analysis, parental smoking was the only significant risk factor for recurrent cough only, with an OR of 1.9 (95% CI, 1.1 to 3.5). In contrast, male gender (OR, 3.5; 95% CI, 1.9 to 6.6), maternal allergy (OR, 2.3; 95% CI, 1.2 to 4.2), wheezing LRIs in early life (OR, 4.0; 95% CI, 2.2 to 7.3), and high IgE level at age 6 years (OR, 2.4; 95% CI, 1.3 to 4.3) were all significant risks for recurrent cough with wheeze, compared to those with neither symptom. These results indicate that not all recurrent coughs are cough variant asthma.

Some retrospective studies have suggested that children with a history of croup may have an increased risk of developing asthma, atopy, or decreased pulmonary function.[60,61] The data gathered in the TCRS were

ideal to prospectively assess the long-term outcome of physician-diagnosed croup in early life. Fifteen percent of children had croup in the first 3 years of life; 10% of these also had wheezing, either with the croup (78%) or as a separate episode (22%); the remaining 5% had croup with no wheezing; 36% had an LRI other than croup, whereas 48% had no LRI.[62] No association was found between markers of atopy during the school years and croup in early life. However, children who had croup with wheeze and those with other LRIs had up to 3 to 4 times the risk of subsequent persistent wheeze and significantly lower levels of lung function in their first, sixth, and eleventh years compared with those with no LRI. Conversely, those with croup without wheeze had significantly higher inspiratory resistance before having an LRI compared with the other groups. These results suggest that croup is a heterogeneous disease, and that children younger than 3 years who present with croup may or may not be at increased risk of subsequent wheezing depending on the initial lower airway involvement, and pre-/post-illness abnormalities in lung function.

At the time of an LRI information was obtained on whether otitis media was also present. A total of 4757 otitis media episodes were recorded in record checks of 1013 infants in the first 3 years of life, 1961 of which were in the first year of life. Breast-feeding was found to be protective,[63] whereas environmental tobacco smoke was a risk factor.[64] Of the 1013 infants followed for their entire first year, 476 (47%) had at least one episode of otitis media and 169 (17%) had recurrent otitis media, defined as at least 3 episodes, 1 month apart, during any 6-month interval in the first year of life. Increasing duration and exclusivity of breast-feeding were associated with a significant decrease in the total otitis media episodes in the first and second 6 months of life and with a decreased risk of recurrent otitis media and nonrecurrent otitis media in the first year of life, independent of other risk factors considered. Infants who were breast-fed but received supplements before 4 months of age had approximately three fourths the risk of recurrent otitis media compared with the reference group who were not breast-fed at all or for less than 4 months. Those infants who were breast-fed exclusively for at least 4 months had one half the risk, and those breast-fed exclusively for 6 or more months had roughly one third the risk of developing recurrent otitis media. Heavy maternal smoking, 20 or more cigarettes per day, was a significant risk factor for recurrent otitis media (OR, 1.8; 95% CI, 1.0 to 3.1) but not for nonrecurrent otitis media, after controlling for other risk factors. In addition, if the infant weighed less than the mean weight (3.5 kg) at birth, heavy maternal smoking was associated with a 3-fold risk for recurrent otitis media (OR, 3.3; 95% CI, 1.7 to 6.4), after controlling for other risk factors.

Infantile colic, a common problem during the first months of life in otherwise healthy, thriving infants, is of unknown origin. Allergy to cow's milk protein has been implicated,[65] suggesting that children with a history of infantile colic may be at increased risk for developing asthma or atopy. In the CRS population there was no increased risk for asthma or wheeze at preschool and school ages for the 9% of infants with a pediatrician diagnosis of colic during the first 2 months of life.[66] There was no association between various markers of allergy (eg, allergic rhinitis, skin tests, total serum IgE) and colic. In addition, we found no relation between colic and breast- or formula-feeding (including cow's milk vs soy-based) in infancy.

WHEEZING SYNDROMES AND ASTHMA

One of the most important findings of the TCRS has been the description of distinct wheezing phenotypes that occur during childhood (Table VI).[15] Although there was the suspicion both from clinical practice and from clinical studies that not all children who wheezed at different times during the growing years had the same pathophysiology, it was only with further analyses of data from the TCRS that these different phenotypes were more extensively characterized. As a result, 3 main syndromes have been described (Fig 6).

Transient infant wheezers

Many children who wheeze during the first 2 to 3 years of life have only a few such episodes and do not wheeze after the age of 3 years. More than 80% of children who wheeze during the first year of life fall under this category; approximately 60% of those wheezing in the second year and 30% to 40% of those wheezing in the third year also belong in this group. These children, when characterized prospectively, are not more likely to have a family history of asthma, and they are not more likely to have atopic dermatitis, eosinophilia, high levels of IgE, or any other marker of an allergic diathesis (Table VI). The main risk factors for this condition, as found in the TCRS, are low levels of lung function before any LRI develops, maternal smoking during pregnancy, and a younger mother.[11] An important finding of the TCRS was that the lower levels of lung function these children had at birth, relative to their peers, improve with time but do not "catch up" with those of children who never wheezed during their growing years (Fig 5). This group of children were also not more likely to wheeze at the ages of 11 and 16 years when compared with children who had no reports of wheezing during the first 6 years of life.

What the fate of these children will be in adult life is difficult to predict, but they may be at increased risk of developing chronic obstructive pulmonary disease, particularly if they start smoking, because of smaller airways.

Nonatopic wheezers

A second group of children continue to wheeze beyond the third year of life after having had an LRI in early life. This group, which we initially called persistent wheezers, is in itself heterogeneous. Approximately 60% of these children are atopic at the age of 6 years, and about 40% are nonatopic.[15] The TCRS allowed us to study these nonatopic wheezers in relation to the etiolo-

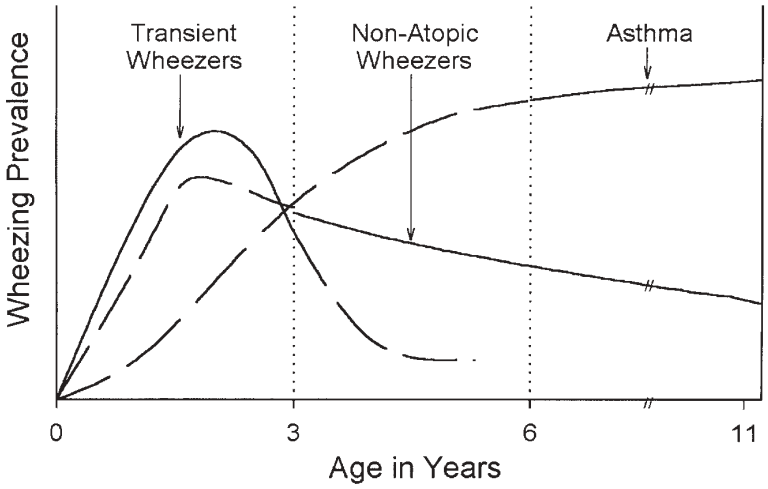

FIG 6. Hypothetical peak prevalence by age for the 3 different wheezing phenotypes. The prevalence for each age interval should be the area under the curve. This does not imply that the groups are exclusive. (Modification [with permission] of Figure 2 in: Stein RT, Holberg CJ, Morgan WJ, Wright AL, Lombardi E, Taussig LM, et al. Peak flow variability, methacholine responsiveness and atopy as markers for detecting different wheezing phenotypes in childhood. Thorax 1997;52:946-52).

TABLE VI. Factors associated with the wheezing phenotypes

	Never wheezed	Transient early wheezing (first 3 y only)	Late onset wheezing (only after 3 y)	Persistent wheezing (< 3 y and at 6)
Percent of total (number)	51.5% (425)	19.9% (164)	15.0% (124)	13.7% (113)
V'_{max} FRC (mL/s) in infancy [n]	123.3 [n = 67]	70.6 [n = 21]*	107.1 [n = 21]	104.6 [n = 16]
(95% CI)	(110.0-138.0)	(52.2-93.8)	(87.5-129.6)	(73.6-144.5)
V'_{max} FRC (mL/s) at age 6 [n]	1262.1 [260]	1097.7 [104]	1174.9 [81]	1069.7 [81]*
(95% CI)	(1217-1308)	(1035-1164)	(1111-1241)	(907-1146)
Total serum IgE (IU/mL) at 9 mo	3.4	3.7	3.8	5.2*
(95% CI)	(3.0-3.9)	(3.1-4.4)	(2.9-5.0)	(3.8-7.2)
Total serum IgE (IU/mL) at 6 y	28.1	31.0	42.1	65.6*
(95% CI)	(22.4-35.3)	(22.3-43.1)	(26.6-66.0)	(45.3-94.4)

*$P < .01$ for comparison with children who never wheezed.
Adapted from Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life: relation with lung function, total serum IgE levels and skin test reactivity to allergens. N Engl J Med 1995;332:133-8.

gy of their LRI in early life.[52] We found that children who had an RSV-LRI were 3 to 5 times more likely to wheeze at the age of 6 years, but this increased risk decreased significantly with age and was almost nonsignificant by the age of 13 years. Other viruses showed similar trends, albeit less consistent than those of RSV-LRI because of small numbers. Of interest was the fact that children who had an RSV-LRI in early life and continued to wheeze beyond the age of 3 years were not more likely to be atopic than other children.[52] The most important difference between this group and children who did not have an RSV-LRI was their lower levels of lung function measured at the ages of 6 and 11 years. Moreover, at the age of 11, a bronchodilator was given to these children, and the results were compared with those children who did not have an RSV-LRI. It was found that children with a history of RSV-LRI were much more likely to show a response to a bronchodilator, and, in fact, their lower levels of lung function completely reversed after bronchodilator, after which time FEV_1 was not significantly different in this group as compared to children who did not have RSV-LRIs.

These results suggested that nonatopic wheezers are probably more likely to develop acute airway obstruction in relation to viral infection because they have an alteration in the control of airway tone that determines this increased risk, and this abnormality in tone may decrease with age. Whether this alteration is present before birth or is the consequence of the RSV-LRI cannot, unfortunately, be determined from the TCRS data.

Atopic wheezers

As several other studies have shown during the last 20 years, the TCRS confirmed that most children who will go on to develop atopic asthma have their first symptoms during the first 6 years of life. Of interest was the fact that in Tucson, contrary to other environments, it was sensitization against *Alternaria* that showed the strongest association with this form of wheezing.[42] It was also of interest that this group of children could be divided into 2

subgroups: early atopic wheezers (who are the majority of what we have called in the past persistent wheezers), ie, those whose symptoms started during the first 3 years of life, and late atopic wheezers (whom in the past we have called late wheezers), ie, whose symptoms started after that age. Both groups were equally likely to be sensitized at the age of 6 years against common aeroallergens, but it was the group whose symptoms started before 3 years of age who showed the lowest levels of lung function at the ages of 6 and 11 years, and it was also this group who showed the highest levels of IgE at the ages of 6 and 11. It thus appears from these studies that, during the first 3 years of life, early initiation of symptoms and perhaps early allergic sensitization may be very important risk factors for more severe disease and for significantly higher deficits in lung function in individuals who develop recurrent episodes of airway obstruction.

ASTHMA PREDICTIVE INDEX

The above discussion has stressed the importance of developing methods to distinguish atopic wheezers from other infants and young children who wheeze in early life but are not destined to have the chronic, more persistent form of asthma-like symptoms. It is possible that, in the future, genetic markers will be used to perform this task. No such markers are yet available, however, and there was the need to test for the predictive capacity of a variety of phenotypic markers that could be used in everyday practice by asthma caregivers. We tested several such markers, all ascertained during the first years of life, and developed an Asthma Predictive Index.[67] To be positive for this index, children needed to have reports of recurrent episodes of wheezing during the previous year and either 1 of 2 major criteria (atopic dermatitis as diagnosed by a physician or physician-diagnosed parental asthma) or 2 minor criteria (peripheral blood eosinophilia, wheezing apart from colds, or physician-diagnosed allergic rhinitis). More than three fourths of all children with a positive index had symptoms consistent with active asthma at least once between the ages of 6 and 13 years, whereas 68% of those with a negative index never had symptoms consistent with active asthma during the school years. We concluded that the subsequent development of asthma can be predicted with reasonable accuracy by using simple, clinically based parameters.

FUTURE STUDIES

During the last 22 years, the TCRS has shown new information for our understanding of the natural history of wheezing phenotypes and asthma during the first years of life. The availability of such a wealth of information regarding events occurring during this crucial period for the development of asthma and allergies will continue to provide the basis of future studies in the TCRS. Areas of focus for the next 5 to 10 years include the following:

1. What factors occurring during childhood determine persistence of asthma beyond the growing years and into early adult life? Several studies have addressed this issue, but all started follow-up during the early school years. Our interest is to determine whether and how various factors, especially atopy, present in infancy and the preschool years can influence the way in which asthma remits, relapses, or persists during early adult years.
2. What is the role of genetic factors in the persistence of asthma into early adult life? The availability of a vast database on environmental factors that can potentially influence the persistence of asthma beyond the childhood years will allow us to determine potential interactions between these factors and genetic markers in many potential asthma-related genes that are being extensively studied in this population.
3. What are the determinants of rapid decline of lung function during the early adult years? Availability of longitudinal data starting at birth will allow us to address this very important issue. It is well-known that losses in lung function that occur during the plateau phase or early during the physiologic decline in lung function with age are very important determinants of subsequent risk for chronic obstructive pulmonary disease. The way in which exposures in early life interact with genetic factors and with the course of asthma and allergies during childhood to determine lung function in early adult life has not been thoroughly studied, and the TCRS is ideal to address these issues.
4. What are the risk factors for incident asthma during the early adult years? Longitudinal studies have suggested that a small number of subjects develop asthma symptoms for the first time during early adulthood, but in most of these studies follow-up started during the school years. The TCRS is the first such study in which follow-up was started at birth, and we will thus have data available that will allow us to determine the role of various types of wheezing in early life and other events occurring during childhood in determining asthma of apparent adult onset.

As can be seen from these few examples, the TCRS intends to continue to provide the caregivers of individuals with asthma and the scientific community with important information regarding the natural history of and the risk factors for recurrent airway obstruction and chronic obstructive pulmonary disease. We are convinced that these studies will allow us in the upcoming years to better design strategies for the primary and secondary prevention of asthma and perhaps will also allow us to address the beginnings of chronic obstructive pulmonary disease, which is today one of the 5 main causes of death in the United States.

A large number of people have been involved with this study during the past 22 years. We thank these technicians, fellows, graduate students, post-docs, statisticians, typists, et cetera, for all of their assistance. Special mention needs to be made of the study nurses, Bonnie Presbrey, Marilyn Smith Lindell, and Lydia de la Ossa, who have been involved in the study for many years. We also wish to thank Group Health Medical Associates pediatricians, who were most instrumental and helpful in enrolling the neonates and their families and obtaining the well-child and acute lower respiratory tract illness data.

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MINI-SYMPOSIUM: COHORT STUDIES

What have we learned from the Tucson Children's Respiratory Study?

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KEYWORDS
asthma, atopy, wheezing, skin tests, bronchial responsiveness

Summary The Tucson Children's Respiratory Study was the first longitudinal assessment of the natural history of asthma in which children were enrolled at birth. Over 1200 children were originally included and over 800 were still participating at age 13. The study has provided general indications about the most important risk factors for and the prognosis of different phenotypes associated with recurrent airway obstruction during childhood. The most important conclusion from the study is that asthma is a heterogeneous disease, with different predominant expressions at different ages. The form of the disease that is associated with atopy is not very frequent in early life, but becomes preponderant during the school years. However, this form is more persistent and is associated with significant deficits in lung function growth up to age 11. Up to two-thirds of infants who wheeze have a transient form of recurrent airway obstruction associated with low premorbid lung function. Many children who wheeze during the preschool years do so only during viral infections. These children usually have a history of wheezing due to respiratory syncytial virus during early life and low levels of lung function during the school years. Understanding the different asthma phenotypes of childhood will provide new clues for strategies for the primary prevention of the disease.

INTRODUCTION

During the 1970s, an observation was made that changed the way chronic obstructive pulmonary disease (COPD) would be understood for the rest of the century: subjects who had COPD in adult life were more likely to recall respiratory troubles during childhood than those who did not have such illnesses.[1,2] Although in these initial studies information on events occurring during the first years of life was obtained by self completed questionnaires and was thus prone to be biased by preferential recall,[3] the results suggested that these early events could influence the risk of the development of COPD. Almost at the same time that these seminal observations were published, studies of infants and young children with confirmed lower respiratory tract illnesses (LRIs) mainly due to the respiratory syncytial virus (RSV) were found to have diminished levels of lung function many years after their original episodes.[4] This observation seemed to provide strong support for the contention that some early infections could damage the airways, the lungs, or both, thus establishing a potential mechanism for the association between LRI and COPD.

Because of the potential biases, this information could only be considered suggestive. It was clear that cohort studies were needed in which data collection about LRI was obtained starting in the neonatal period, thus avoiding preferential recall. The Tucson group headed by Benjamin Burrows had developed considerable experience in longitudinal studies of COPD[5] and it was thus natural that such cohort studies were first proposed by this group. The result was the Tucson Children's Respiratory Study (CRS), headed by L.M. Taussig, A.L. Wright and W.J. Morgan, in which over 1200 children were enrolled at birth, between 1980 and 1984.[6,7] The CRS is presently the longest ongoing cohort study of children enrolled at birth and it has been followed by several other such studies, in different environments and settings. In this paper, I will summarise my personal view of the main issues that the CRS has addressed in relation to the natural history of childhood asthma. This analysis cannot be considered exhaustive,

given the large number of questions that we have attempted to tackle using CRS data. Moreover, I do not intend a comprehensive review of each of the issues discussed. My premise is that, although considerable advances have been made in our understanding of the natural history of and risk factors for recurrent airway obstruction in children and adults, many issues remain unresolved and should be the matter of considerable scrutiny in the next few years.

ASSOCIATION BETWEEN LUNG FUNCTION AND LRI IN EARLY LIFE

The first objective of the CRS was to detect and evaluate most LRIs occurring during the first 3 years of life. This time frame was arbitrarily chosen: the main objective was to avoid missing LRIs occurring after the first 2 years which could also have an influence on respiratory outcome. Several hundred such episodes were assessed and, in most cases, information directly derived by the paediatricians regarding each LRI (including screening for wheezing, stridor and crackles by auscultation) became available. Virological tests were performed for most LRIs detected and blood samples were obtained at the time of the acute illness and during convalescence. Initially the study design did not include assessment of lung function before the development of the first LRIs, because no lung function methods were available that could be used in an epidemiological setting. Towards the end of the recruitment process, however, the chest compression technique to obtain partial maximum flow-volume curves was developed[8] and this test, together with assessments of the tidal breathing curve and of responses to forced oscillation was applied to over 100 of the last group of children enrolled in the study. These children were studied between the ages of 1 and 6 months of age and before any recorded LRI. The observation was then made that children who had an LRI during the first year of life had significantly lower mean values for several parameters obtained using the three techniques of assessing lung function described above.[9] Moreover, when data for the first 3 years of life were assessed, the association became clearer, especially for parameters obtained from maximal flow-volume loops.[10] Results of several longitudinal studies performed in the subsequent years confirmed this finding,[11–13] although not all studies confirmed each of those findings and the physiological correlates of several (if not all) of the indices used in the original studies are still a matter of considerable controversy.[14] Addressing these issues goes beyond the scope of this paper but I believe it is now justified to conclude that the association between early postnatal alterations in lung and airway function (albeit still ill-defined) and the subsequent development of LRI during the first years of life has been firmly established.

ASTHMA AND WHEEZING DURING THE FIRST 6 YEARS OF LIFE

The observation that lower levels of lung function present shortly after birth preceded and predicted the development of LRI suggested a potential explanation for the link between LRI and subsequent recurrent episodes of airway obstruction and lower levels of lung function. Thus, if lung function tracked with age, then children born with lower lung function would still have low lung function several years later. They would also be more prone to LRI, because their narrower airways would be more prone to become obstructed during LRI, especially in the first months of life.[15] It thus became important to assess the respiratory outcome during the early school years (both in terms of symptoms and of lung function) of children who had LRI. What we found had probably been suspected for the previous 50 years[16] but never confirmed in a controlled longitudinal study: 60% of children who had LRI in early life had no reported wheezing episodes by the age of 6.[17] We later showed that the great majority of these children were still asymptomatic at ages 11 and 16.[18] We called them "transient wheezers", and this appellation is now used by many in the literature and in clinical practice. An important observation was that at age 6 and again using partial expiratory flow-volume loops but this time obtained from voluntary manoeuvres, transient wheezers still showed lower mean levels of lung function than children who did not wheeze during the first 3 years of life. At least for this group, the hypothesis that diminished lung function at birth could explain the link between LRI and deficits in spirometric parameters later in life seemed to be supported by our longitudinal data.

However, the group of children who wheezed during LRI in early life and were still wheezing at age 6 (dubbed "persistent wheezers") did not fit this hypothesis. Their levels of lung function were slightly, but not significantly, lower shortly after birth from those of children who did not wheeze during the first 3 years of life, but were significantly reduced by the age of 6.[17] This suggested that the reduced levels of lung function observed at age 6 could be the result either of the LRIs themselves, or of other processes occurring in these children's airways or lungs. It was interesting to observe that 60% of persistent wheezers were already skin test positive to at least one local aeroallergen by age 6, compared to less than 20% of non-wheezers. Moreover, mean total serum IgE levels measured as early as at 9 months of age were significantly higher among persistent wheezers than among non-wheezers, whereas transient wheezers had mean 9 month serum IgE levels that were similar to those of non-wheezers. These results suggested that in at least a proportion of persistent wheezers, activation of the immune system towards the production of IgE could have already occurred as early as the first year of life.

IMMUNE RESPONSES DURING LRI AND SUBSEQUENT WHEEZING

To test that hypothesis we used blood samples obtained at the time of the first acute episode of LRI and during the convalescent period for that same LRI in children who went on to become either persistent wheezers or transient wheezers.[19] We measured total serum IgE levels and performed eosinophil counts on both occasions in both groups and in a third group of children who never wheezed but who had LRIs diagnosed as either pneumonia or croup.

We found that children who would go on to become persistent wheezers had significantly higher levels of IgE at the time of the acute illness compared with the sample obtained during convalescence. Transient wheezers and children who had non-wheezing LRIs had IgE levels that were similar during the time of the acute illness to those observed during the convalescent period. In the case of eosinophil counts, children who would be later classified as transient wheezers had significantly lower counts at the time of the acute illness than during convalescence. A similar eosinopaenic response was observed in children who had non-wheezing LRIs. By contrast, children who would later be classified as persistent wheezers had no eosinopaenic response during the acute phase of the illness.[19] These findings suggested that, already at the time of the first acute LRI associated with wheezing, persistent wheezers showed, as a group, acute responses to what, in most cases, was a viral infection that were characterised by increased IgE production and a blunting of the normal eosinopaenic response to these infections. Since both IgE production and eosinophil responses are mediated by cytokines of the Th2-like-type, the data supported the hypothesis that these responses were established very early in life in individuals who would go on to develop atopy-related asthma.

All these data suggest that, apart from transient wheezing of infancy, two other syndromes appear to co-exist between the ages of 2 and 11. A significant group of children has wheezing that is unrelated to allergic sensitisation. This form of the disease is more benign and of a better prognosis: wheezing episodes had remitted in most of these children by the age of 11–13 years.[20] By contrast, children sensitised to local aeroallergens and especially to *Alternaria*, had more persistent symptoms and by the age of 11–13, the great majority of wheezing children were sensitised to at least one local aeroallergen.

ASTHMA AND *ALTERNARIA* IN A DESERT ENVIRONMENT

During the 1980s influential writers proposed the hypothesis that exposure to certain specific aeroallergens could be causative in the development of asthma.[21,22] The data seemed to be quite overwhelming: many studies performed in coastal areas had consistently showed that sensitisation to house dust mites was almost universally present among school-age children with asthma. The concept emerged that avoidance of exposure to house dust mites could become a successful strategy for the prevention of asthma.[23] There was an implicit assumption in this concept: in places where exposure to house dust mites was low, asthma should also be less prevalent. Tucson seemed to be a good environment in which to test this hypothesis. Although mites have been isolated from house dust samples in the area, levels of exposure are considerably lower than those observed in coastal regions.[24] However, we found that the prevalence of asthma and of current wheezing at age 6 and 11 was even higher in Tucson than in other areas of the USA where similar studies had been performed. As expected, children born and raised in Tucson were less likely to be sensitised against house dust mites compared with those raised in coastal areas. We found that a different allergen seemed to have "taken the place" (so to speak) of house dust mites: sensitisation to *Alternaria*, a mould present during all seasons both indoors and outdoors in the Tucson area, was most strongly associated with asthma and explained most of the relationship between the latter and aeroallergen sensitisation.[24] Similar findings were concomitantly reported by Peat *et al.*[25] in the desert regions of Australia. Moreover, children who became sensitised to *Alternaria* by age 6 were most likely to have persistent asthma by age 11,[20] in much the same way as had been reported by Peat *et al.*[26] for early sensitisation to house dust mites in coastal regions of Australia.

Based on these findings, we concluded that the concept that most cases of childhood atopic asthma are caused by sensitisation to a single allergen could not be further sustained.[27] We speculated that the basic immunological derangement in atopic asthma had to be less specific and it had to predispose to the development of sensitisation to many different aeroallergens that may be present early in life in the area where the future asthmatic child was raised.

DEVELOPMENT OF IFN-γ RESPONSES IN EARLY LIFE

The nature of this derangement is still intensely debated. In the early 1990s studies performed in different parts of the world suggested that children with a family history of allergies were more likely to have impaired IFN-γ responses at birth compared with those who had no such family history.[28] During that same period it was reported that two types of murine T-helper cells could be identified based on the cytokines they were able to produce: Th-1 cells produced IFN-γ and interleukin-2 (IL-2) but not IL-4 or IL-13, and Th-2 cells produced IL-4 and IL-13 but not IFN-γ.[29] Since IL-4 and IL-13 are the only cytokines able to signal B cells for the production of IgE and production of these

cytokines by Th-2 cells is inhibited by IFN-γ *in-vitro*, it was plausible to surmise that the development of Th-2 responses (and, thus, IgE antibodies) to aeroallergens very early in life could be regulated by the production of IFN-γ by immune cells during this period. As part of the CRS protocol, such IFN-γ responses were assessed in cord blood and at age 9 months in a subsample of enrolled children. Children with stronger IFN-γ responses at age 9 months (but not in cord blood) were more likely to develop sensitisation against local aeroallergens than those with weaker responses. The association was particularly strong for sensitisation to *Alternaria*.[30] In addition, children whose parents were atopic had lower IFN-γ responses at 9 months of age than those whose parents were not atopic. These data thus suggested that genetic and environmental factors that enhance IFN-γ responses during the first years of life could prevent the development of early allergic sensitisation and, by this mechanism, decrease the likelihood of asthma incidence.

DAY CARE, SIBLING EXPOSURE AND WHEEZING DURING CHILDHOOD

After these studies were published, this particular area of research became particularly active. The hypothesis was proposed by us and others that microbial burden during early life could contribute to the maturation of Th-1 responses.[31] A thorough review of these issues goes beyond the scope of this paper. The initial impetus for these ideas was provided by Strachan,[32] who observed an inverse association between number of older siblings in the household and prevalence of allergic rhinitis in a large cohort in the United Kingdom. Shortly thereafter, researchers from Germany[33] observed that children taken to day care during the first months of life were less likely to have allergy-related outcomes during the school years. To explain the results of both studies, the authors speculated that the incidence of infections could be higher in infants exposed to other children, either at home or in day care centres and that these infections could play a role in the prevention of allergies and asthma. To test this hypothesis, we assessed data from the CRS to relate day care attendance and presence of older siblings at home during the first months of life to the subsequent development of recurrent wheezing episodes at different ages during childhood.[34] We found that children who were taken to day care during the first 6 months of life or who had two or more older siblings at home were more likely to have recurrent episodes of wheezing at 2 and 3 years of age. However, starting at the age of 6 years, infants who were exposed to other children in the first 6 months of life were significantly less likely to have recurrent episodes of wheezing than those who were not exposed. The data supported the hypothesis that different mechanisms could be involved in the pathogenesis of asthma-like symptoms during childhood. During the early years, allergic mechanisms seem to play a role in a minority of children. The most important factor determining wheezing episodes seems to be viral infections. It is thus not surprising that an increased incidence of viral infections associated with exposure to other children increases the incidence of wheezing episodes in early life. By the school years, however, most wheezing children are atopic. Exposure to other children very early in life appeared to be protective in these children.

OUTCOME OF RSV-LRIs: NON-ATOPIC PERSISTENT WHEEZING

In the above discussion I have stressed the evidence derived from the CRS that suggests that the Th-2-like responses, characteristic of atopic asthma, are established very early in life. However, as mentioned earlier, only 60% of persistent wheezers showed positive skin test reactivity to aeroallergens at age 6. Both this observation and clinical experience suggested to us that, during the toddler and early school years, atopy-associated asthma could co-exist with a different form of the disease that was not associated with sensitisation to local aeroallergens. To test this hypothesis, we used two approaches. In the first approach, we subdivided children with asthma-like symptoms at age 6 into two groups:[20] those who were sensitised to *Alternaria* by that age and those who were not. The analysis revealed that children who were sensitised to *Alternaria* showed significantly different epidemiology, natural history and outcomes compared with those who were not sensitised. *Alternaria*-sensitised asthmatics had started having symptoms later in life (after the first year), had more severe symptoms, were more likely to have high serum IgE levels and were more likely to be wheezing at the age of 11. Conversely, *Alternaria*-negative asthmatics often started having wheezing episodes during the first year of life and were significantly less likely to still be having wheezing episodes at the age of 11 years. In a second type of analysis,[35] we studied the outcome of the first LRI due to RSV or to other viruses, most of which occurred during the first year of life. We found that RSV-LRI was a significant risk factor for wheezing (both frequent and infrequent) at the age of 6 years. However, this risk significantly decreased with age and was only borderline significant by the age of 13. Similar, although less consistent, results were found for LRIs due to other viruses or for those in which no viruses were isolated. No association was found between LRIs due to RSV or to any other viruses and the likelihood of becoming sensitised to local aeroallergens at either age 6 or age 11. Children who had had RSV-LRIs were found to have significantly lower levels of size-corrected forced expiratory volume in the first second (FEV_1). However, when FEV_1 was studied after administration of two puffs of albuterol, no significant differences were found between children who had had RSV-LRIs and those who had not.

CONCLUSIONS

In this brief summary I have tried to stress the most important analyses of data from the Tucson Children's Respiratory Study (CRS) that were intended to elucidate the natural history of asthma during early life. These results have provided a framework within which to understand the complex nature of asthma-like symptoms during the first years of life. I am convinced that the Tucson CRS has provided the paediatrician, the paediatric allergist and the paediatric pulmonologist with new elements to understand the risk factors for, and the natural history of, wheezing episodes during the early childhood years. It has also provided information for parents and caregivers about the prognosis of these episodes and the elements that are associated with an increased likelihood of recurrent wheezing later in life. Finally, we hope that our findings will help in the development of strategies for the primary and secondary prevention of a group of illnessess that affect millions of children in every corner of the world.

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